

Compendium of Public Comments on the
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
November 19, 2014 – March 29, 2015

Name	Comment #	Page #
Aalto, Mary	46	46
Abernathy, Shannon.....	151	153
Adams, Stephen.....	185.....	188
AdvaMed	220.....	261
Allan, Gary	105.....	107
American Heart Association	228	356
American Physical Therapy Association	210	235
American Society of Clinical Oncology	207	225
American Thoracic Society	229	362
Andrews, Brian	165	167
Andrews, Jane.....	18	18
Antonuccio, David	170	172
Ashman, Michael	119	121
Asquith, Helen	93	95
Association of American Medical Colleges.....	230.....	366
ASTRO	222.....	333
Avey, Marc.....	172	174
Bagnall, Kara	158	160
Balaam, Deidre	7	7
Barros, Enrique	146	148
Bauer, Felix	162.....	164
Beecroft, Simon	155	157
Blanc, Francis	96	98
Bobrow, Martin	183	186
Bolton, Monica	62	63
Borkusmalorkus, Riley	137	139
Boyd, Karen	51	51
Boyer, Denis.....	133	135
Brigham and Women’s Hospital/ Massachusetts General Hospital	223	336
Bryant, Nita.....	19	19
Bulat, Berislav	147	149
Bumgardner, Derek	179	182
Campbell, Kristina.....	186.....	189
Carneiro, Ilona	136	138
CDISC	204.....	212
Chamberlayne, John	192	196
Coffey, Matt.....	66	67
Coleman, Mike.....	154	156
Corness, Raymond	65.....	66
Council on Governmental Relations	225	346
Cullen, Breda	128	130
Cunha-Cruz, Joana	10	10
Curlin, Marion.....	36	36

Compendium of Public Comments on the
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
November 19, 2014 – March 29, 2015

Name	Comment #	Page #
Dahl, Viktor	81	82
Dam, Peter.....	169.....	171
Dang, Tran	80	81
Davidson, James	55	55
Davis, Alicia.....	61.....	62
Davis, Alicia.....	61.....	62
Davis, Catherine.....	212	240
DeGraaff, Cindy	17	17
diBucchianico, Marilena	28	28
Domin, Sabine	23	23
Donnay, Albert.....	203	211
Edwards, Peter	194	198
Ellis, Rob	101.....	103
Endocrine Society	202	208
European Association of Hospital Pharmacists	224.....	341
Evans, Ifor	84.....	85
Federation of American Societies for Experimental Biology	213	242
Frangioni, John	191	194
Frasineanu, Cristina	4	4
Frouard, Pierre.....	90	92
Gannon, Mel	31	31
Geldsetzer, Pascal.....	173	176
Giguet, Alban	113.....	115
Girling, Dave	25	25
González y Garcia, Alberto	164	166
Goodall, Maria	148	150
Goodwin, Joshua	175	178
Graham, William.....	166	168
Greenbaum, Carla.....	197	201
Gregory, Pat.....	85.....	86
Hakemian, Sami	130	132
Halpin, Stephen	160	162
Hamidi, Wan	76	77
Hanau, Ryan.....	41	41
Harris, Chelsea.....	71	72
Harris, Duncan	59	60
Hay, James	64	65
Hayes, Samantha	53	53
Healey, Jon.....	68	69
Hendry, Jane	11	11
Henrich, Alexander	60	61
Henriksen, Stephanie.....	72	73
Holmes, Joe	182.....	185

Compendium of Public Comments on the
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
November 19, 2014 – March 29, 2015

Name	Comment #	Page #
Holtedahl, Robin	161	163
Hunn, Rosa.....	89.....	91
Hush, Michele.....	108	110
Ingram, Cameron.....	5	5
Ivins, Frank.....	138.....	140
Jackson, Oliver	116	118
Jani, Anant	107	109
Janosik, Miro.....	142	144
Johnson, Jennie	145	147
Johnson, Paul.....	57	58
Johnstone, Christopher	3	3
Jones, John	150.....	152
Karpinski, Richard	63	64
Keenor, Garry	54	54
Kelsey, Peter	29.....	29
Kerrison, Nick.....	187.....	190
Kimble, Adam	157	159
Kirk, Jenny.....	196.....	200
Kloster, Nels.....	45	45
Koort, Olaf	190	193
Kovari, Michael	21	21
Kumar, Gourav.....	131	133
Kumar, Raahul	69	71
Kumpare, Aino	198	203
Kurth, Alexander.....	189.....	192
Lareau, Sondra.....	98	100
Laughlin, Carla	50	50
Lee, Kirsty	91.....	93
Lee, Michele	44	44
Lempert, Thomas.....	110.....	112
Lester, Carolyn.....	83	84
Lipka, Jennifer.....	181.....	184
Llanusa-Cestero, Renée	209	232
Lochhead, Guy	12	12
London, Kathy.....	34	34
MacAuslan, Joel	214	245
MacIntyre, Donald	139	141
Mahon, Clare	129	131
Manas, Sikdar	104	106
Marcotte, Jeanette	16	16
Markos, Andrew	188	191
Markowitz, John	117	119
Martin, Steven	99	101

Compendium of Public Comments on the
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
November 19, 2014 – March 29, 2015

Name	Comment #	Page #
Massachusetts General Hospital/ Brigham and Women’s Hospital	223	336
Matti	149	151
Maxwell, Steve	153	155
Mayo Clinic	221	328
McCartney, Mike	114	116
McCavit, Kim.....	26	26
McCorkell, Peter	132	134
McCormick, John	74	75
McGill, Dilys	103	105
McLean Hospital	227	354
McMahon, Elizabeth.....	6	6
Medical Device Manufacturer’s Association	233	382
Medical Library Association/Association of Academic Health Sciences Libraries	208	230
Millaa, Jay	120.....	122
Minty, Fay	94	96
Mohamed, Lakhali	123	125
Montani, Michael Francis	156	158
Morgan, Dan.....	73.....	74
Moseley, D. V.....	193	197
Naik, Vinay	75	76
NEPI Foundation	37	37
New England Journal of Medicine	235	388
Newcombe, Robert.....	126	128
Newman, Kyle.....	13	13
Nichols, Linda.....	177.....	180
Nunn, David	92	94
O’Mahony, Cian	180	183
O’Reilly, David.....	167	169
Oddie, Sam	121	123
Oliveto, Alison	200	205
Olson, Don	9	9
Orlowitz, Jake	88	89
Ossebaard, Hans	163	165
Packham, D. E.	159	161
Parker, James.....	118.....	120
Parker, Malcolm	109	111
Partners Healthcare.....	218	255
Patchick, Emma	102	104
Platt, Mark	115	117
Poizner, Tracy	49.....	49
Public, Jean	56	56
Puljak, Livia	111	113

Compendium of Public Comments on the
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
November 19, 2014 – March 29, 2015

Name	Comment #	Page #
Purdom, Karen.....	199	204
Q., Janice.....	216	250
Rashidi, Batool.....	152	154
Ravitz, Evan.....	52	52
Rawlings, Jeff	127	129
Raychaudhuri, Clare	43	43
Revans, Rosalind.....	178	181
Reynolds, Brett	1	1
Richard.....	201	207
Ring, Nadja.....	82	83
Robinson, Ash	48	48
Rogers, Steve	47	47
Rook, Chris.....	77	78
Roper, Kim	140	142
Rostron, Cath	32	32
Ryan, Chris	2	2
Ryan, Rebecca.....	67	68
Sacks, Lucille	58	59
Salman, Rustam	22	22
Samour, Patricia	106	108
Samuels, Lucy	134	136
Santa Barbara, Joanna	42	42
Saunders, Mary.....	33	33
Schellenberg, Susan.....	125	127
Schelling, Franz	79	80
Seed, Paul	27	27
Semlyen, Anna.....	86	87
Sense About Science.....	226	349
Setiawan, Marco.....	174	177
Shanahan, Daniel.....	184	187
Smith, Donald	15	15
Stevenson, Pam & Bill.....	143	145
Stewardly.....	236	389
Sulhunt, Adam	205	215
Tanner, Polly.....	38	38
Ter Riet, Gerben	20	20
The Children’s Hospital of Philadelphia		
Research Institute	231	372
Thompson, Matthew	135	137
Thornicroft, Graham.....	215	247
Torres, David.....	14	14
Turcotte, Fernand.....	8	8
Tweedale, Tony	39	39
University of California, San Francisco	206	216

Compendium of Public Comments on the
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
November 19, 2014 – March 29, 2015

Name	Comment #	Page #
University of California Systemwide.....	237	394
University of Florida	217	252
University of Michigan.....	232	375
Urquhart, David	112	114
Vahey, Nigel.....	100	102
Van Someren, Laurie	95	97
Vandenberg, Steve	97	99
Verhelle, Katy	124	126
Verhovez, Andrea	40	40
Von Delft, Tilman.....	144	146
Wade, Ainley.....	171.....	173
Waller, Liz	168	170
Wanger, Sharon.....	30	30
West, Michael.....	141	143
Wicks, Chris	176	179
Wideman, Nonie.....	78	79
Wilson, Diane.....	234	384
Winslow, Robin.....	122	124
Wood, Phil	24	24
Yale University Open Data Access Project/ Yale- New Haven Hospital’s Center for Outcomes Research and Evaluation.....	211	238
Zerbe, Janet	35	35
Zubizarreta, Jose.....	195	199

From: [Brett Reynolds](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for trial registration
Date: Tuesday, November 25, 2014 1:08:04 PM

I support requiring all the trials funded by the NIH to be registered and to report results.

--

The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336.

From: [Chris Ryan](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All Trials should be reported
Date: Tuesday, November 25, 2014 1:08:46 PM

I support the policy that all clinical trials funded by the NIH need to be registered and to report results.

From: [Christopher Johnstone](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials reporting
Date: Tuesday, November 25, 2014 1:14:11 PM

Dear Sir/Madam

I fully support all the trials you fund to be registered and to fully report all results

Best wishes

Dr Chris Johnstone
GP / Family Doctor
Paisley
Scotland

The Quality Outcomes Framework must be destroyed

From: [Cristina Frasineanu](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support
Date: Tuesday, November 25, 2014 1:16:06 PM

Dear Sirs,

I support you in requiring all the trials it funds to be registered and to report results.

Best regards,
Cristina Frasineanu

From: [Cameron Ingram](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: In support of clinical trial reporting
Date: Tuesday, November 25, 2014 1:20:31 PM

To whom it may concern,

Having worked in the biomedical devices industry, NIH-funded research labs at premier medical institutions, and now as a medical student dependent on past, present, and future clinical trials of integrity, I fully support the NIH's attempts to make clinical trials more transparent. Reporting on results is more to me than just about being open to the public, who give the very dollars that funds the NIH, but it is also about patient safety and effectiveness in advancements in biomedical science and medical research. What better way to show the American people that their hard-earned dollars are being put to work than to let them know about the very things that they pay for, including a system that lets them know when something may go wrong. Adverse events are currently under-reported, and making it compulsory to report results associated with all clinical trials could help with this problem. Just as importantly, promoting an environment of free and open communication is a much more effective way to communicate negative results, in which current clinical trials may NOT have a positive outcome for new technologies. This information is just as important as realizing how beneficial a new treatment is, and requiring such communication would be the only sure way for medical professionals, patients, and the public to know more about the very medical treatment, outcomes, and research in which we are all using.

Yours in Health and Solidarity!
-Cameron

Cameron M. Ingram
University of Cincinnati
College of Medicine, Class of 2018
[NHSC Scholar](#)
[Volunteer Clinical Intern](#)
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+1 (937) 470-5746

From: [Liz McMahon](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: In Support of Clinical Trial Reporting
Date: Tuesday, November 25, 2014 1:23:38 PM

As a licensed psychologist trained in research methodology and following evidence-based best practices, I strongly support the HHS and NIH proposals to expand requirements to register clinical trials and report results, and to make this a condition of research funding.

Thank you.

Elizabeth McMahon, PhD
CA Lic # PSY 6737

From: [Deirdre Balaam](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: CLINICAL TRIALS
Date: Tuesday, November 25, 2014 1:30:40 PM

Dear Sirs

I support the NIH requiring all the trials it funds to be registered, and to report results.

Yours sincerely

Deirdre Balaam

From: [Fernand Turcotte](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Reporting all trials and all results
Date: Tuesday, November 25, 2014 1:33:53 PM

I support entirely the initiative of NIH to require reporting of all trials and all results.

Fernand Turcotte, MD,MPH, FRCPC

Fernand.Turcotte@msp.ulaval.ca

From: [Dr. Don Olson](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Please make registration and reporting a condition of funding
Date: Tuesday, November 25, 2014 1:37:18 PM

Dear NIH:

I applaud the new an upcoming transparency for trials and support the NIH proposal to make registration and reporting a condition of funding. Please continue your work towards making transparency a reality in all future trials for the betterment of those who benefit from these trials.

Thank you,
Don

Don Olson, DC, FASBE, DACS
'A' STREET CLINIC OF CHIROPRACTIC, PLLC
1020 A St SE
Suite 4
Auburn Washington 98002
Ph: 253-939-0909
<dondc@reachone.com>

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From: [Joana Cunha-Cruz](#)
To: [clinicaltrials.disseminationpolicy](#)
Date: Tuesday, November 25, 2014 1:37:19 PM

I support that you require all the trials to be registered and to report results.
Thanks,
Joana

From: [jane hendry](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Trials to be made public
Date: Tuesday, November 25, 2014 1:46:30 PM

All the trials you fund and support should be made public

Sent from my iPad

From: [Guy Lochhead](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials consultation
Date: Tuesday, November 25, 2014 1:50:32 PM

I am e-mailing to register my voice in support of the proposed increase transparency around clinical trials.

Yours hopefully,
Guy Lochhead

From: [Kyle](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support clinical trials dissemination policy
Date: Tuesday, November 25, 2014 1:50:34 PM

NIH,

I am writing to tell you that I support this policy. It will prevent work being unnecessary repeated, and can provide critical information to other trials and studies. A negative result is just as important as a positive one.

Kyle

From: [David Torres](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Tuesday, November 25, 2014 1:53:35 PM

Dear NIH

I support requiring all the trials you fund to be registered and to report complete results.

--

Dr. David Torres
Santiago, Chile

From: [Donald Smith](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Please report all trials publicly
Date: Tuesday, November 25, 2014 1:59:13 PM

Hello,

Please report all the trials that you do publicly so that everyone knows the results.

Regards,

D Smith

From: [Jeanette Marcotte](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Expansion of Funding Requirements
Date: Tuesday, November 25, 2014 2:00:19 PM

To whom it may concern:

As a concerned global citizen and member of the science community I am writing to state my support of your proposed expansions requiring funded trials to be registered and report their results. Transparency of clinical trials is critical on a local and world stage. Information sharing is the best way to push the science forward and I am very pleased to see you moving in that direction.

Thanks for doing your part to make the world a healthier place. Keep up the good work!

--

Jeanette Marcotte P.Geo.

From: [Cindy DeGraaff](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trial transparency
Date: Tuesday, November 25, 2014 2:02:53 PM

As the NIH is a government sponsored agency, accountable to the American people, all of the clinical trials sponsored by the NIH should be made available to the American people for review. Transparency in clinical drug trials is an important measure in ensuring honesty and integrity in the drug trial process. The only way to do so, is to make all information available to the people ultimately paying for these trials, all of the citizens who may have an interest in their outcomes.

Thank you.

Cindy DeGraaff, RN

From: [Jane Andrews](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registration and Results reporting for Clinical Trials
Date: Tuesday, November 25, 2014 2:05:22 PM

Greetings to whom it may concern at the NIH:

I am an internal medicine physician in New Orleans, Louisiana. I recently was made aware of the proposal to ensure that all clinical trials be registered, and report their results. Wanted to let you know that I agree- this should certainly be a condition of research funding, and bravo to you all for proposing it! High time!

Sincerely,

Jane Andrews, MD, MPH
Clinical Instructor of Medicine, Tulane University

--

Jane Andrews
Cell: 513-807-0394

From: [Nita L Bryant](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registration and Dissemination
Date: Tuesday, November 25, 2014 2:06:50 PM

I am very much in favor of requiring all clinical trials be registered and for all results to be reported.

Nita Bryant, Ph.D.
Behavioral & Social Sciences Research Librarian
Library Liaison, Institute for Drug and Alcohol Studies
Academic Outreach [JBC, room 111a]
James Branch Cabell Library
Richmond, VA 23284-2033
Phone: 804-828-6651

From: [G. ter Riet](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All trials must be reported
Date: Tuesday, November 25, 2014 2:16:18 PM

To whom it may concern,

I fully support the initiatives, as described by Hudson in JAMA last week, to ensure full reporting of all (NIH sponsored) trial results. That said, It is a sobering thought that the bias in the scientific evidence base on existing hypotheses will only slowly approach zero as the biased evidence gets mixed with more and more unbiased evidence if your initiative succeeds. Only for completely novel hypotheses the initiatives help to establish an unbiased evidence base rightaway.

Kind regards,

Gerben ter Riet, MD PhD Associate Professor

Hon. Senior Lecturer, Queen Mary Univ London

Dept. General Practice - Academic Medical Center

Room J2-116, 1105 AZ Amsterdam, The NLS

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From: [Michael Kovari](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Tuesday, November 25, 2014 2:18:32 PM

Just a quick note to say how much I support the views of Francis Collins, Director of NIH, "We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health."

I strongly support requiring that all the trials funded by NIH should be registered and *a//* the results reported promptly.

--
Michael Kovari
12 Clifton Drive
Abingdon
OX14 1ET
(01235) 553-338

From: [Rustam Al-Shahi Salman](#)
To: [clinicaltrials.disseminationpolicy](#)
Date: Tuesday, November 25, 2014 2:25:31 PM

Dear colleague

I support the NIH requiring all the trials it funds to be registered and to report results.

Best wishes,

Rustam

Rustam Al-Shahi Salman

Professor of clinical neurology and MRC senior clinical fellow, University of Edinburgh
Honorary consultant neurologist, NHS Lothian

Skype: rustamatwork

Twitter: @BleedingStroke @edinburghstroke

Facebook: <https://www.facebook.com/bleedingstroke>

Research website: <http://www.dcn.ed.ac.uk/rush>

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regular gift <http://edin.ac/1iNmwqV>

The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336.

From: [Sabine Domin](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Tuesday, November 25, 2014 2:27:14 PM

Dear NHI, please make it a requirement of your clinical trials funding that all results must be published. And use your power that this should also be the rule for all clinical trials regardless of who is paying for them. Take the Chance to be a Role model for European and German health authorities, too! Thank you! Dr. Domin, MD

From: [Phil Wood](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: reporting and registering clinical trials research
Date: Tuesday, November 25, 2014 2:39:18 PM

To Whom It Concerns,
I am writing in support of the policy that all clinical trials be both registered and reported. Thank you for your consideration.
Phil Wood
Columbia, MO 65203

From: [Dave Girling](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials
Date: Tuesday, November 25, 2014 2:41:10 PM

I fully support any requirement to publish all clinical trials and their results even where the results are negative.

David Girling

From: [Kim Mccavit](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trials transparency
Date: Tuesday, November 25, 2014 2:50:06 PM

Dear Sirs;

I'm sending this email to voice my support for requiring all trials that you fund to register and report results publicly, whether negative or positive.

thanks for your attention

Kim McCavit

From: [Seed, Paul](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Full reporting of RCTs
Date: Tuesday, November 25, 2014 2:56:44 PM
Attachments: [image003.png](#)

Dear people,

The selective reporting of results from randomised controlled trials is not just a waste of the resources and expertise that went into collecting the information. By effectively suppressing results that do not suit their business model, unscrupulous companies may be able to sell inferior or dangerous medicines and other clinical products.

I am greatly encouraged by news of plans involving the HHS and NIH to require full transparency of results as a condition of research funding. I trust you will resist lobbying to water down the proposals to suit commercial advantage.

Yours faithfully,

[Paul T Seed, Senior Lecturer in Medical Statistics,](#)

Division of Women's Health, Faculty of Life Sciences & Medicine, King's College London
 Women's Health Academic Centre, King's Health Partners
 020 7188 3642,
paul.seed@kcl.ac.uk,
<https://kclpure.kcl.ac.uk/portal/en/persons/paul-seed%280f9a5fec-1160-4da4-8eff-a2747678d894%29.html>
 Paul T Seed is partly funded by Tommy's (Registered charity no. 1060508)

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From: [marilena di buchianico](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support AllTrials
Date: Tuesday, November 25, 2014 3:05:02 PM

I support a change in the regulations requiring all the trials the NIH funds to be registered and to report results.

Please make it happen, we need it.

Marilena Di Bucchianico, PhD

From: [Peter Kelsey](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: new policy
Date: Tuesday, November 25, 2014 3:06:00 PM

To Whom it May Concern:

The US Department of Health and Human Services (HHS) and National Institutes of Health (NIH) have announced proposals to expand requirements to register clinical trials and report results, and to make that a condition of research funding.

I completely support these expanded requirements. Incomplete trial reporting is nothing less than fraud.

Peter Kelsey, LICSW

From: [Sharon Wanger](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials Reporting
Date: Tuesday, November 25, 2014 3:08:49 PM

I strongly support your requiring all trials that you fund be registered and results reported. This will enable both physicians and patients to be able to make more informed decisions and will improve health care in this countryl.

--

Sharon Wanger

From: [Mel Gannon](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support the proposal requiring all the trials you fund be registered and to report results.
Date: Tuesday, November 25, 2014 3:09:58 PM

From: [Cath Rostron](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Register trials and report results
Date: Tuesday, November 25, 2014 3:11:19 PM

Please continue to support that the trials you fund need to be registered and to report results. This will benefit us all,
Regards,
Cath Rostron

From: [Mary Saunders](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for registration of trials and for open dissemination of trial data
Date: Tuesday, November 25, 2014 3:13:38 PM

Greetings clinicaltrials.desseminationpolicy@mail.nih.gov

I am writing as an individual patient and cancer survivor to support registration of trials and open sharing of results. I believe this will soon be a world standard, and I believe the U.S. should comply now rather than later.

I have received e-mail information that Glaxo is already complying.

U.S. based corporations need to do the same without delay.

Cheers,

Mary Saunders
Portland, Oregon

From: [Kathy London](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trials
Date: Tuesday, November 25, 2014 3:14:34 PM

Please require all the trials you fund be registered and the results reported. Thank you.

Kathy London

visit my author blog
under my pen name at
<http://www.katerauner.wordpress.com>

From: [Janet Zerbe](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: trial registration and reporting
Date: Tuesday, November 25, 2014 3:16:29 PM

I support your efforts to register trials and to report results of trials. I am a former NIH patient and participant in a clinical trial.
Janet Zerbe

From: [Marion](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Policy Needed to best benefit public health
Date: Tuesday, November 25, 2014 3:16:49 PM

Please make it policy that all clinical trials NIH funds be registered and that all results be reported to the public. We owe it to our fellow citizens to make sure that this valuable information can and will be used to the greatest benefit to the health of all.

Thank you,

Marion Curlin

From: [Mikael Hoffmann](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for your work on registering and reporting results from clinical trials
Date: Tuesday, November 25, 2014 3:16:50 PM

The NEPI foundation fully supports your initiative in requiring registering and reporting the results from all clinical trials funded through NIH. This is an important issue in order to enhance transparency in clinical trials internationally.

Best regards

Mikael Hoffmann
CEO, The NEPI Foundation - (www.nepi.net)

Tel: 070-608 20 28

mikael.hoffmann@nepi.net

Twitter @lakemedel

The NEPI foundation was initiated and funded by the Swedish Parliament in 1993 with the aim to support the development of pharmacoepidemiology, health economics, and drug information.

From: [Polly](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Tuesday, November 25, 2014 3:17:27 PM

Our daughter has been diagnosed with a rare condition. She and her specialists need to have access to all the information that can be made available through the in depth reporting of clinical trials. Thank you for your efforts in making this happen.

Polly Tanner
New Zealand

Sent from my iPad

From: [Tony Tweedale](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: yes to your clinical trials reporting publically
Date: Thursday, November 27, 2014 4:44:09 AM

Please do ensure that your funding requires trial conductors to be entirely transparent about their research.

Tony Tweedale, MS
16445 Collinson Av.
Eastpointe MI 48021-3023
ttweed03@yahoo.com
tel.: +1-586-776-8356 Skype: ttweed03
VOIP: +1-586-441-3595

From: [andrea.verhovez](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support clinical trial reporting measures in the US
Date: Tuesday, November 25, 2014 3:26:31 PM

My name is Andrea Verhovez, I am a physician currently working in the Italian National Health Service and support the proposal that all the trials funded by HHS and NIH should be registered and required to report the results completely.
Yours sincerely

Andrea Verhovez

From: [Ryan H](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Expand requirements to register clinical trials
Date: Tuesday, November 25, 2014 3:32:46 PM

I support requiring all the trials the NIH funds to be registered and to report results.

Ryan Hanau

--

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From: [Joanna Santa Barbara](#)
To: [clinicaltrials.disseminationpolicy](#)
Date: Tuesday, November 25, 2014 3:37:45 PM

I support the registration and reporting of results of all clinical trials.

Joanna Santa Barbara

MB.BS, FRANZCP, FRCP(C), O.Ont.,

New Zealand.

From: [Clare Raychaudhuri](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registering clinical trials
Date: Tuesday, November 25, 2014 3:41:57 PM

Dear Sir or Madam,

I am writing you to express my support for the proposals to expand requirements regarding registering clinical trials and reporting results, to make that a condition of research funding. This is essential so that Doctors and regulators can make informed decisions about treatments, saving patients lives.

Kind regards

Clare

From: [michele.lee](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Requiring Results of Clinical Trials to be Available to the Public
Date: Tuesday, November 25, 2014 3:46:50 PM

As a cancer patient who does a lot of research, I am continually incredulous and frustrated at the number of trials whose results are never published. We need this information and it is very useful and relevant in continued research. Not only should results be available for public consumption, but also there is no excuse for spending public dollars to duplicate research that is kept hidden.

Regards,
Michele Lee

From: [Nels Kloster](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trials
Date: Tuesday, November 25, 2014 3:46:53 PM

I am writing to support requiring all clinical trials funded by NIH be registered and have results reported.

--

Nels A Kloster, MD
PO Box 404
Marlboro, VT 05344
802.579.7980 Office
802.258.9802 Fax Brattleboro
802.440.9805 Fax Bennington
802.258.7549 Cell

If you have received this email by mistake, this message and/or attachments may contain confidential information not meant for you. If you are not the intended recipient, please notify me right away and delete this email and attachments from your files. Thank you.

From: [Mary Aalto](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials
Date: Tuesday, November 25, 2014 3:47:48 PM

I support that the NIH in require all clinical trials that it funds be registered and that trial investigators report all research findings regardless of the results.

Thanks,
Mary Aalto

From: [Steve Rogers](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Consultation on clinical trials
Date: Tuesday, November 25, 2014 3:49:07 PM

I support NIH requiring all the trials it funds to be registered and to report results.

From: [Ash Robinson](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials transparency
Date: Tuesday, November 25, 2014 3:54:16 PM

Hi there,

I want to add my name to the growing group of people who feel it is only right that the results of clinical trials funded by you are made openly available to the public.

Kind Regards,
Ash

www.dollarmixbag.com

From: [tracy poizner](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: registration of trials
Date: Tuesday, November 25, 2014 4:07:38 PM

As a Canadian citizen, I know that my government looks to U.S. policymakers for leadership on a broad range of topics, particularly where strong lobby forces are in play that can potentially influence legislation. I ask you to provide the kind of leadership that can benefit the whole world on the issue of mandatory registration and reporting of all clinical trials.

There is no need to go into why this is in the urgent public interest. Please do the right thing.

Sincerely,
Tracy Poizner

--

"Aude Sapere"

Tracy Poizner, Classical Homeopath
www.tracypoizner.com
tpoizner@gmail.com
519-635-1656

From: [Carla Laughlin](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All clinical trial results should be reported!
Date: Tuesday, November 25, 2014 4:30:17 PM

This is serious

Carla Laughlin

Sent from my iPhone

From: [Karen Boyd](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Require clinical trials to be registered and results reported
Date: Tuesday, November 25, 2014 4:39:26 PM

To whom it may concern

I am writing to show my support for the US Department of Health and Human Services and National Institute of Health plans to expand requirements to register clinical trials. I fully support the plans you are considering regarding requirement that all the trials you funds to be registered and to report results.

thank you
Karen Boyd

Karen Boyd MSc, RD
Regional Executive Director
Alberta and the Territories Region | Dietitians of Canada
179 Hubman Landing | Canmore, AB | T1W 3L3
T 403 675 2693 | E karen.boyd@dietitians.ca

From: eravitz@gmail.com on behalf of [Evan Ravitz](#)
To: clinicaltrials.disseminationpolicy
Subject: Publish all trials results
Date: Tuesday, November 25, 2014 4:43:55 PM

To whom it may concern,

To prevent death and illness from side effects, to prevent inferior medicines from becoming standard, and to prevent unethical companies from getting more money to buy corruption, ALL clinical trials of medicines and devices should be published.

Evan Ravitz

POB 1873

Kamuela, HI 96743

[Evan Ravitz Freelance Editing](#) (303)923-5918

[Gates of Paradise](#) hot springs backpacking trips

[Iridescent cloud](#) cards, prints, iPad covers, etc.

Vote the "mock" out of democracy at [Vote.org](#)!

Warning! NSA analysts could be reading this email. And because there's hardly any accountability, we have no idea how they may use it. If that bothers you, [click here to do something about it.](#)

From: lsudaw@sahayes.co.uk on behalf of [Samantha Hayes](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support
Date: Tuesday, November 25, 2014 4:46:56 PM

Dear NIH

I support you requiring all funds to be registered for clinical trials and all trails registered and results reported.

Kind Regards

Samantha Hayes
Clinical Scientist
Brighton, UK

From: [Garry Keenor](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Tuesday, November 25, 2014 4:50:12 PM

I strongly support your proposals to increase transparency and availability of all trials data. We owe it to patients and trial participants to do this. Please defend your proposals!

regards,

Garry Keenor

From: [James Davidson \(ADHB\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: all clinical trials must be registered and rreported
Date: Tuesday, November 25, 2014 4:50:29 PM

Dear sir/madam

I wish to register my support for a policy which would make it **mandatory for all NIH-funded trials to be registered and results reported.**

sincerely

Dr. James Davidson
Clinical Head
Department of Chemical Pathology
Labplus
Auckland City Hospital
Auckland, New Zealand
tel +64-9-3074949 ext 22052
mobile 021-774-656

From: [Jean Public](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Fw: public ocmment on clinical trial revision Support clinical trial reporting measures in the US
Date: Tuesday, November 25, 2014 4:52:53 PM

----- Forwarded Message -----

From: Jean Public <jeanpublic1@yahoo.com>
To: "clinicaltrials.disseminationpolicy@mil.nih.gov" <clinicaltrials.disseminationpolicy@mil.nih.gov>; "americanvoices@mail.house.gov" <americanvoices@mail.house.gov>; "vicepresident@whitehouse.gov" <vicepresident@whitehouse.gov>; "rush.holt@mail.house.gov" <rush.holt@mail.house.gov>; "info@taxpayer.net" <info@taxpayer.net>
Sent: Tuesday, November 25, 2014 4:42 PM
Subject: Fw: public ocmment on clinical trial revision Support clinical trial reporting measures in the US

i want this agency to know i certainly do support expansion into clinical trials so that the public gets full report on all trials, and that the profiteer cant just turn in the "good" trials that favor hsi product. the american public is getting totally scammed by the way this law is so lax and negligent in protecvtion for the public. this commeten is for the public record please receipt. jean publi jeanpublic1@yahoo.com

Dear Friends

Last month, many of you supported the WHO's plan to call for the results of all clinical trials to be reported. Now we all need to support proposals from the US Government to improve clinical trial transparency there.

The US Department of Health and Human Services (HHS) and National Institutes of Health (NIH) have announced proposals to expand requirements to register clinical trials and report results, and to make that a condition of research funding. This is a significant and potentially transformative step in the battle for clinical trial transparency.

Francis Collins, Director of NIH, said, "We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health." [Read more about the proposals and comments from Ben Goldacre and other AllTrials supporters here.](#)

We have to make sure HHS and NIH don't water down these strong proposals.

1. [Tell HHS that you support it expanding the law](#) so that more trials have to be registered and reported.
2. Email clinicaltrials.disseminationpolicy@mail.nih.gov to tell NIH that you support it requiring all the trials it funds to be registered and to report results.

Both consultations run until 19th February 2015 and are open to everyone, not just US citizens. We are working on our responses now and will share them with you soon.

Best

Ian

--

Ian Bushfield

Campaigns Support Officer

Sense About Science: *Science and evidence in the hands of the public*

AllTrials: [Web](#) | [Twitter](#) | [Facebook](#)

Please let us know if you prefer not to receive e-mails from us: [Unsubscribe](#)

Please note this is an automated operation.

14A Clerkenwell Green

LONDON, EC1R 0DP

United Kingdom

From: [Paul Johnson](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials policy
Date: Tuesday, November 25, 2014 4:56:23 PM

To whom it may concern,

I am a British citizen and a patient who, with some reluctance, is taking a statin medication. I have tried to find out more about statin side effects but have found it difficult to find independent (not industry funded) research that has been able to gain satisfactory access to clinical trials data, including adverse effects. Therefore, **I urge the NIH to make it a condition of funding that all trials you fund must be registered, must report results in full no matter whether the trial is regarded as a success or is abandoned early, and must make all data available to independent researchers.**

Many thanks for taking the time to consider my request.

Paul Johnson
109 Middle Lane, Whitley, Melksham, Wilts, SN12 8QR, England

—

Paul Johnson
Copywriter
Pen and Ink Communication
+44 (0)7866 314197
+44 (0)1225 790703
www.pen-ink.co.uk

From: [Lucille. Sacks](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: REPORT RESULTS OF ALL TRIALS
Date: Tuesday, November 25, 2014 5:06:12 PM

It is extremely important that you register all trials and report the results. Research and the public demand complete and accurate reporting

Thank you.

Lucille Sacks
Brooklyn, NY 11201

From: [Duncan Harris](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for clinical trial registration and reporting
Date: Tuesday, November 25, 2014 5:41:23 PM

Dear Sirs,

I write to urge you to be steadfast in your stance that all the trials you fund must to be registered and must report results. This is probably the most important thing we can do for future healthcare so we know which treatments work and for which people.

Duncan Harris
33 Alpraham Crescent
Upton
Chester
CH2 1QX
United Kingdom

From: [Alexander Henrich](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Supporting clinical trial reporting measures
Date: Tuesday, November 25, 2014 5:51:56 PM

Dear NIH,
I support it requiring all the trials you fund to be registered and to report results.

Sincerely,
Dr. Alexander Henrich
Burgwedeltwiete 17
22457 Hamburg
Germany

From: [Davis, Alicia](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support of Proposal for Clinical Trial Transparency
Date: Tuesday, November 25, 2014 6:01:17 PM
Attachments: [image001.png](#)

Hello,

I am writing to voice my support of the current proposal by the NIH to require that all the trials it funds are registered and to report results. I think that transparency is critical to scientific success as the cost to reinvent the wheel is large. It will also ensure that all patients that participate in clinical trials are contributing to the pool of knowledge, as many of them have to complete extra testing and visits to be on trials. It is an ethical, efficient, and much needed move forward.

Thanks for your consideration,

Alicia M. Davis, BS, BA | Clinical Research Coordinator
Radiation Therapy | Neurological Oncology | Gynecological Oncology
Cancer Clinical Trials Office
1665 Aurora Court | Room 3200, MSF 700 | Aurora, CO 80045
720-848-0608 | Pager: 303-266-1057 | Fax: 720-848-0486



From: [Monica Bolton](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trials proposals
Date: Tuesday, November 25, 2014 6:07:29 PM

Dear NIH

I strongly support the proposals now out for consultation requiring all the trials you fund to be registered and for the investigators to report results. Please do not water these proposals down - public money should be used in a fully accountable way. These proposals will lead to greater transparency and so to increased patient safety.

Yours

Monica Bolton

From: [Richard Karpinski](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Report results of clinical trials?
Date: Tuesday, November 25, 2014 6:17:53 PM

Yes!

Richard Karpinski, Nitpicker extraordinaire
6521 Raymond St. 148 Sequoia Circle
Oakland, CA 94609 Santa Rosa, CA 95401
Home: 707-546-6760
<http://nitpicker.pbwiki.com/> <http://CureCancerNow.WikiFoundry.com/>
Mission: to bring known cancer cures to a clinic near you, soon.

From: [James Hay](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Drug trials
Date: Tuesday, November 25, 2014 6:34:46 PM

I strongly support the proposed HHS/NIS drug trial reporting guidelines. It is time to stop reporting only the trials that make new drugs look good. Suppressing results is antithetical to science and good medicine.

James H. Hay

From: [Raymond Corness](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials
Date: Tuesday, November 25, 2014 6:39:01 PM

I support the NIH requiring all the trials it funds to be registered and to report results.,
Raymond Corness

From: [Matt Coffey](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support of all Funded Trials Being Published
Date: Tuesday, November 25, 2014 6:49:15 PM

I support of all clinical trials funded by your organisation having their data made publicly available.

Best regards,
Matt Coffey
32 Charles Knott Gardens
Southampton
SO152TF
UK

From: [Rebecca Ryan](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support for requirement for all trials you fund to be registered and to report results
Date: Tuesday, November 25, 2014 6:51:15 PM

Thank you for making important steps towards transparency

From: [Jon Healey](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Transparency in .drug trials
Date: Tuesday, November 25, 2014 7:03:34 PM

I support the requirement that all trials you fund be registered and results reported publicly.
Thank you.
Jon Healey

From: [Raahul Kumar](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trial reports
Date: Tuesday, November 25, 2014 8:04:08 PM

Clinical trials are very important, yet we often don't hear about the failed results. Please share all the data, so that people can make informed choices about drugs and other medical treatments.
Set the data free!

All trials must be registered and report results, otherwise don't fund them!

Regards,

Raahul.

From: [C M Garratt](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: ALL TRIALS campaign
Date: Tuesday, November 25, 2014 8:16:38 PM

Dear Sir / Madam,

I write strongly to support the publication of all trial data, including the raw data, for use by the scientific community. Allowing publication only of trials which support a thesis is damaging and dishonest. The development of evidence-based practice demands practice-based evidence of a high order, otherwise we are just following commercial interests.

Richard Garratt
MB ChB DRCOG DA FRCS MRCGP DHSM

From: [Chelsea Harris](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Transparency and registration in research
Date: Tuesday, November 25, 2014 8:38:33 PM

To whom it may concern

Just wanted to add to the multitude of voices saying I support the NIH in regards to making it compulsory to register their trials, and for research to be made as transparent as possible. For the good of the people!

Regards
Chelsea Harris
NZ

From: [Stephanie Henriksen](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All trials NIH funds to be registered and reported
Date: Tuesday, November 25, 2014 8:44:31 PM

Dear Sir:

I support requiring all trials for new drugs and medical devices be registered and reported. Minnesota Farmers Union added a new resolution to their policy to that effect in recent years. With the help of NIH and FDA, I hope to live to see this come to pass.

Stephanie Henriksen
Stone Hill Farm
PO Box 267
Dundas, MN 55019
507-301-9998 cell

From: [Dan Morgan](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Register and Report Trials
Date: Tuesday, November 25, 2014 8:52:58 PM

Howdy,

As a taxpayer, I help fund these trials. Therefore, I support you requiring all the trials NIH funds to be registered and that the results are reported.

Dan Morgan
3601 gold crest ln
Rosamond, CA
93560
661.401.9129

From: [John McCormick](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support and thanks
Date: Tuesday, November 25, 2014 10:35:33 PM

Hello

Please accept this Email supporting your excellent proposal requiring all trials you fund to be registered and results reported. This openness and transparency is an important step in informing consumer choice and should be lauded.

Kind regards

John McCormick

From: [Vinay Naik](#)
To: [clinicaltrials.disseminationpolicy](#)
Date: Tuesday, November 25, 2014 10:47:42 PM

Hello,

I fully support the NIH policy to require all the trials that it funds to be registered and for them to report results that are then made freely accessible to the public and in particular to researchers for their studies.

Thank you.

Sincerely,

Vinay Naik.

From: [wan hamidi](#)
To: [clinicaltrials.disseminationpolicy](#)
Date: Tuesday, November 25, 2014 11:11:10 PM

dear NIH

i support all clinical trials to report its funds and results to be registered to NIH

thank you

--

Wan Hamidi Wan Sulaiman
B.Pharm (USM), R.Ph. (2860), MMPS.

From: [Chris Rook](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registration of all clinical trials
Date: Tuesday, November 25, 2014 11:13:43 PM

Dear sir or madam,

I am writing to strongly support the motion that ALL clinical trials be registered and results reported. This is without doubt in the interests of the public and should be strongly pursued.

Kind Regards,

Dr Chris Rook
General Practitioner
BSc(Hons) MBBS DFFP FRACGP

Globe Medical | the experts
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(W) www.globemedical.com.au

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From: [Nonie Wideman](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: trial funding
Date: Tuesday, November 25, 2014 11:15:10 PM

I support requiring all the trials funded to be registered and to report results. We must maximize learning from all trials , deemed successful or not.

--

Nonie Wideman wishes peace,health, and prosperity to you and yours. May the wind be at your back and joy in your heart.

From: [Franz Schelling](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: "lost" clinical trial results
Date: Wednesday, November 26, 2014 12:36:44 AM

Sir or Madam,

It is amazing how selective publishing of only positive trial observations of supposedly prophylactic but at best symptomatically effective medications has spread. Having watched an aggravation of such side effect denialling and whitewashing of trial results of all the years of my medical carreer, I implore you that you require all the trials you fund to be registered and their results to be reported.

Sincerely,

Franz Schelling, M.D. of 1970

From: [Tran, Dang](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for clinical trial transparency
Date: Wednesday, November 26, 2014 1:59:29 AM

I support requiring all clinical trials be registered and have results reported.

Dang Tran
Doctor of Pharmacy Candidate, 2017
University of California, San Francisco
dang.tran@ucsf.edu

From: [Viktor Dahl](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support
Date: Wednesday, November 26, 2014 3:36:56 AM

Hi,

I support that all clinical trials that you fund should be registered and that the results should be reported.

Best,

Viktor Dahl, MD, PhD

From: [Nadja Ring](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Register clinical trials!
Date: Wednesday, November 26, 2014 4:01:41 AM

Dear NIH,

I think it is a great step to require that all trials funded by the NIH must be registered and results must be reported. Please don't back down on these expectations! Publishing results saves lives!

Thank you,
Nadja Ring
PhD Student

From: [Carolyn Lester \(Public Health Wales\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Open information
Date: Wednesday, November 26, 2014 4:12:40 AM

In the interests of patients worldwide, please ensure that all trials you fund are registered and that the results are reported in full.

Carolyn Lester
Principal Public Health Specialist
Public Health Wales, Temple of Peace and Health, Cathays Park Cardiff, CF103NW
Iechyd Cyhoeddus Cymru Cenedlaethol Cymru, Teml Heddwch ac Iechyd, Parc
Cathays, Caerdydd, CF10 3NW

Tel: 02920 402465 FAX: 02920 402504 Email: carolyn.lester@wales.nhs.uk
Internet: www.publichealthwales.org
Intranet: nww.publichealthwales.wales.nhs.uk

From: [Ifor Evans2 \(Hywel Dda Health Board - Pembrokeshire Locality Office\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: trials registration
Date: Wednesday, November 26, 2014 4:14:31 AM

Hi

I fully support your proposals that all clinical trials be registered and have to report results as a condition of funding.

regards

[Ifor Evans RGN, RMN, MSc.Econ, MBA](#)
[Rheolwr Rhwydwaith Gofal Critigol Canolbarth a Gorllewin Cymru / Mid and West Wales](#)
Critical Care Network Manager
[Bwrdd Iechyd Hywel Dda/ Hywel Dda University Health Board](#)
[Adeilad Springfield/ Springfield Building](#)
[Ysbyty Llwynhegy/ Withybush Hospital](#)
[Hwlford/ Haverfordwest](#)
[Sir Benfro/ Pembrokeshire](#)
SA61 2PZ

Rhif Ffon/ Tel: 07794 053377

e-bost / e-mail: ifor.evans2@wales.nhs.uk

gwefan / web site <http://www.wales.nhs.uk/sites3/home.cfm?orgid=962>

From: pg7576@gmail.com on behalf of [p.g](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Reporting and registering of all clinical trials
Date: Wednesday, November 26, 2014 4:15:41 AM

Dear Sirs

I wish to support a law which would require the reporting and registering of all clinical trials.

Thank you.

Pat Gregory

From: [Anna Semlyen](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All trials
Date: Wednesday, November 26, 2014 4:24:51 AM

I support requiring all the trials you fund to report all results and full data exposure

Anna Semlyen, 20's Plenty for Us Campaign Manager 07572120439
anna.s@20splentyforus.org.uk www.20splentyforus.org @AnnaSemlyen1

From: [Pieter Vandekerckhove](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support clinical trial reporting measures in the US
Date: Wednesday, November 26, 2014 4:58:01 AM

Dear madam, Dear sir,

I am encouraging you to continue your fantastic work and I am strongly supporting you to fund all the trials required to be registered and to report the results of those trials.

Walking the right path is hard, but we know it's right.

Kind regards
Pieter Vandekerckhove

From: [Jake Orlowitz](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Supporting registration and reporting for all clinical trials
Date: Wednesday, November 26, 2014 4:52:50 AM

Dear researchers, regulators, and public health specialists at the NIH,

My name is Jake Orlowitz and I am a board member of Wiki Project Med Foundation. We organize and edit Wikipedia's 30,000 medical articles which receive 200 million views every month. When we write articles on Wikipedia we look to the best published information from large randomly controlled trials, systematic reviews, clinical practice guidelines, and professional society recommendations. Despite our efforts to summarize existing literature, we *know* that we are failing the public because the existing literature does not reflect the full scope of conducted trials, historically or at present. As Ben Goldacre's AllTrials.net initiative has demonstrated, the ability for null findings and exploratory research to simply go unreported creates a perverse incentive for medical research to be cherry-picked and disguised for specific business outcomes.

The solution to this is extremely simple: All trials must be registered and reported. Where possible their full findings must be viewable to the public and patient-level data must be available for secondary analysis. The canard that this will infringe on the intellectual property of pharmaceutical research leads to the alternate and insane conclusion that we are better off when drug companies can conduct 10 trials that show the results they don't like and publish the 1 result that shows the result they do like. A high school statistics student could explain that leads to a corruptible bias and their high school teacher would never accept it. Imagine doing 100 tosses of a coin flip and only publishing the 50 heads results! A perfect coin, wow!! Unfortunately, the perfect coins we are dealing with are the physical and mental health of our sisters and grandfathers and children and ourselves.

This unacceptable situation cannot be allowed to continue. Each country has the power to regulate how clinical research is conducted and reported. On behalf of Wikipedia's 500 million monthly readers, I am personally calling on you to change a broken system to one that serves the goal of recording the sum of all medical knowledge. Your part in that requires that you demand all clinical trials be registered and reported. If you use this power, you will enable us as editors from around the world to do our goal of sharing the sum of all medical knowledge with every person on the planet.

There are few more important ways we can empower humans than giving them complete information which informs their health decisions. I am urging you to change the way that clinical trials are registered and reported so that 100 years from now we are not still walking around with 'perfect coins' in our bodies that hide the truth. Please use your power to ensure the best health outcomes for every person on the planet.

Sincerely,

Jake Orlowitz
Board Member
Wiki Project Med Foundation
<http://meta.wikimedia.org/wiki/WPMED>
wikiprojectmed@gmail.com
484-684-2104

From: [Rosa Hunn](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: AllTrials
Date: Wednesday, November 26, 2014 5:03:09 AM

Dear Sir/Madam,

I am emailing to state that I support all the trials you fund to be registered and to report all results.

Many thanks

Rosa Hunn

RM&G Coordinator |

NIHR Logo

Email. rosa.hunn@nihr.ac.uk | **Telephone.** 0203 328 6723

Address. NIHR Clinical Research Network, 7th Floor, 18 King William Street, London, EC4N 7BP

From: [pierre frouard](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support clinical trial reporting measures in the US
Date: Wednesday, November 26, 2014 5:06:38 AM

Dear NIH

As a caregiver I am committed to better patient care. I spend a lot of my medical time in reducing overmedicalisation and overtreatment, and I am astonished by the overwhelming presence of drug industry in the medical environment.

For all these reasons, I support a rule requiring all the trials funded by the NIH to be registered and to report results.

Pierre Frouard MD
general practitioner
(France)

From: [Kirsty Lee](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Trial reporting
Date: Wednesday, November 26, 2014 5:06:50 AM

I support the requiring of all the trials you fund to be registered and to report results.

Kirsty Lee

Sent from my iPhone

From: [david nunn](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trials dissemination policy
Date: Wednesday, November 26, 2014 5:07:42 AM

Dear Sir or Madam

“We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health.” (Francis Collins, Director of NIH).

I can't see how any reasonable person could disagree with the above. For this reason I support the NIH's move to require all the trials it funds to be registered and to report results.

Best regards,

David Nunn

From: [Helen Asquith](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Response to consultation - support for NIH expansion of requirements to register clinical trials and report results
Date: Wednesday, November 26, 2014 5:10:30 AM

Dear Sir,

I support the commitment by the National Institutes of Health to require all the trials it funds to be registered and to report their results. Please do not water down your current proposals to do so.

Yours faithfully,

Dr Helen Asquith MBBS BSc MAOxon MMPH MFPH
Specialist Registrar in Public Health
Imperial College NHS Trust

From: [Fay](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support the NIH requiring all the trials it funds to be registered and to report results.
Date: Wednesday, November 26, 2014 5:14:07 AM

To Whom it May Concern

I support the NIH requiring all the trials it funds to be registered and to report results.
Without transparency, we receive a fraction of the NIH investment returned.

Dr Fay Minty

9 Manbey Grove
Stratford, London
E15 1EX

Home: 0208 555 5878
Mobile: 07759 759564

Email: fay@loudness.force9.net

<https://www.linkedin.com/in/fayminty>

From: [laurie](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Release results
Date: Wednesday, November 26, 2014 5:16:17 AM

You owe it to those who submit to clinical trials, and to those who will in future benefit from careful use of their results, to make results available as widely as possible. Please give generously!
Thanks,
LvS

--

Laurie van Someren, Aleph One Ltd, The Old Courthouse,
123 High Street, Bottisham, CAMBRIDGE CB25 9BA UK
www.aleph1.co.uk and www.yaffs.net T: 01 223 811679

From: [blanc francis](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support clinical trial reporting measures in the US
Date: Wednesday, November 26, 2014 5:46:24 AM

I support a rule requiring all the trials funded by the NIH to be registered and to report results.

Docteur Francis BLANC ; MD
14 boulevard Maréchal Lannes
81000 ALBI
FRANCE

From: [Steve Vandenberg](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Reporting all Clinical Trials
Date: Wednesday, November 26, 2014 5:46:31 AM

Thank you for moving forward with making available to the public all clinical trial information.

With this kind of reporting, the interests of the people and science will be able to move forward once again. Science and the public good should be the main factor in reporting trials, not the image and "spin" of corporations.

Sent from my iPhone

From: [sondra](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Reporting trial results
Date: Wednesday, November 26, 2014 5:49:09 AM

I support requiring all the trials you funds to be registered and to report results.

Thank you
Sondra Lareau
Kannapolis, NC
7042247002

From: [Steven Martin](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registration and reporting of trials
Date: Wednesday, November 26, 2014 5:50:14 AM
Attachments: [0549D97A-579F-4599-A4B3-2E050F30E83D.png](#)
[466FD12A-714F-4766-8F70-B14E6A1B4A4F.png](#)
[4BFDB2F0-63D4-443C-8CEF-49CE6B76BF70.png](#)

To whom it may concern,

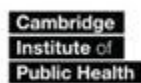
This is an email to to indicate my support for expanding the law so that more trials have to be registered and reported. The expansion of requirements to register clinical trials, report results, and to make that a condition of research funding, is a significant and potentially transformative step in the battle for clinical trial transparency.

Thank you,
Steven

Steven Martin
Research Associate

Institute of Public Health
Forvie Site
University of Cambridge School of Clinical Medicine
Box 113 Cambridge Biomedical Campus
Cambridge
CB2 0SP

Tel: 01223 330317
Email: sm987@medschl.cam.ac.uk
Twitter: @PublicHealthSte



From: [Nigel Vahey](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Compulsory Research Trial Registration & Reporting
Date: Wednesday, November 26, 2014 6:04:43 AM

To whom it may concern,

I am an internationally active academic psychologist from Ireland, and this email is to express my strong support for NIH to require all of the research trials it funds to be registered and publicly reported.

Sincerely,

Nigel

--

Nigel Vahey, BA Hons (Psych) MBPsS PhD (Candidate)
Department of Psychology,
National University of Ireland Maynooth,
Maynooth,
Co. Kildare,
Ireland

From: [Rob Ellis](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trial Reporting
Date: Wednesday, November 26, 2014 6:06:51 AM

In support of the AllTrails/Sense About Science campaign I wish to add my support requiring all the trials to be registered and to report results.

Regards,

Rob Ellis

From: [Emma Patchick](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support the registering and reporting of ALL funded trials
Date: Wednesday, November 26, 2014 6:18:24 AM

Dear NIH,

I previously supported the call to WHO to insist that researchers publish results of ALL trials.

As scientists we are acting fraudulently AND doing a disservice to the advancement of knowledge if we only report 'positive' results. All knowledge is positive, whether it's as expected or not.

I understand you have proposed that you will make the registering and reporting of trials a condition of research funding. I understand it may be difficult to enforce (i.e. how could you 'retract' funding if the results were never written up? Perhaps you could just have the threat of not being considered for future funding as a deterrent). But I am writing to inform you that I fully support this proposal and hope that these strong proposals don't get watered down in the consultation process.

Best regards,
Emma

Emma Patchick
PhD student Psychology

Tel: 0161 275 3530

www.psych-sci.manchester.ac.uk/students/EmmaPatchick

From: [Dilys Mcgill](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Trials to be registered and reported
Date: Wednesday, November 26, 2014 6:22:18 AM

I agree that the NIH should require all the trials it funds to be registered and to report results.

From: [Sikdar Manas \(NHS BRIGHTON AND HOVE CCG\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Please support maximum transparency in clinical trials
Date: Wednesday, November 26, 2014 6:32:26 AM

Please support this.

The US Department of Health and Human Services (HHS) and National Institutes of Health (NIH) have announced proposals to expand requirements to register clinical trials and report results, and to make that a condition of research funding. This is a significant and potentially transformative step in the battle for clinical trial transparency.

Francis Collins, Director of NIH, said, "We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health." [Read more about the proposals and comments from Ben Goldacre and other AllTrials supporters here.](#)

Dr Manas Sikdar

Albion Street Surgery
9 Albion Street
Brighton
BN2 9PS

Tel +441273 601122
Fax+441273 623450

manassikdar@nhs.net

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NHSmail provides an email address for your career in the NHS and can be accessed anywhere

From: [Gary Allan](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support requiring trials to be registered
Date: Wednesday, November 26, 2014 6:50:07 AM

I support complete registration of clinical trials in order to advance science and medicine

Gary Allan

From: [mamipat](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support of trials funded needing registration and reporting
Date: Wednesday, November 26, 2014 6:56:07 AM

Please be advised I support NIH requiring all the trials it funds to be registered and to report results.

Thank you,

Patricia Samour
PO Box 1295
Goodlettsville, TN 37070
mamipat@rocketmail.com

Happy Connecting. Sent from my Sprint Samsung Galaxy S® 5 Sport

From: [Anant Jani](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Requirement for all trials to be registered and to report results.
Date: Wednesday, November 26, 2014 7:32:15 AM

Hi,

I just wanted to send an email to say that I strongly believe that all trials should be registered and researchers should be required to report results.

Thanks,
Anant

From: [Michele Hush](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Report the full results of clinical trials
Date: Wednesday, November 26, 2014 7:49:40 AM

Dear National Institutes of Health,

It is shocking, dangerous and wrong that pharmaceutical companies are able to pick the results that make new drugs seem safe and submit only those.

I support the release of ALL clinical trial results. As NIH Director Francis Collins said, it is a matter of what would provide the greatest benefit to human health.

Sincerely,

Michele Hush

From: [Malcolm Parker](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials proposal
Date: Wednesday, November 26, 2014 7:51:01 AM

I fully support your proposal to require the registration of and the reporting of all results from all of the clinical trials that you fund.

Thank you.

Malcolm Parker
15 Foster Road
Frome, Somerset
BA11 1NX
United Kingdom

From: [Lempert, Thomas](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: data transparency for all clinical trials
Date: Wednesday, November 26, 2014 8:06:15 AM

Dear colleagues at the NIH,

I strongly support your move for registration of clinical trials and compulsory reporting of all data as a prerequisite for rational clinical decision making.

Yours sincerely,

Thomas Lempert

Prof. Dr. med. Thomas Lempert

Chefarzt Abteilung für Neurologie

Schlosspark-Klinik

Heubnerweg 2, 14059 Berlin

Tel.: (030) 3264 - 1158

Fax: (030) 3264- 1150

E-Mail: thomas.lempert@schlosspark-klinik.de

www.schlosspark-klinik.de

From: [Livia Puljak](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All trials should be registered and results reported
Date: Wednesday, November 26, 2014 9:04:58 AM

Dear NIH,

I would like to urge you to require that all trials should be registered and all results reported. Failure to do so costs lives and makes incredible losses to patients. I hope that you will do the right thing.

Sincerely,
prof. Livia Puljak

From: [David Urquhart](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for trial registration
Date: Wednesday, November 26, 2014 9:31:16 AM

Dear NIH,

As a family physician I believe that the best quality evidence available should be used to support medical decision-making. With this in mind, I am writing to state my support for a campaign to have any NIH-funded clinical trials registered with mandatory reporting of results.

Regards,

David Urquhart, MD, CCFP

From: giquet.alban@gmail.com on behalf of [Cabinet Medical Apollinaire](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support clinical trial reporting measures in the US
Date: Wednesday, November 26, 2014 9:38:32 AM

I support a rule requiring all the trials funded by the NIH to be registered and to report results
Dr Alban GIGUET

From: [Mike McCartney](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for trial registration and reporting
Date: Wednesday, November 26, 2014 9:38:43 AM

Dear Sir/Madam,

In the interests of accountability, transparency and scientific integrity I strongly support the requirement that all trials which NIH funds should be registered and should provide reports which are publicly available describing their results.

Kind regards,

Mike McCartney

From: [Mark Platt](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials Funding Proposals
Date: Wednesday, November 26, 2014 10:16:11 AM

I would like you to register my support for you proposal to require all of the trials that NIH funds to be registered and for all of their results to be publicly reported.

Mark Platt
London, UK

From: [Oliver Jackson](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registration and reporting of NIH funded trials
Date: Wednesday, November 26, 2014 10:36:56 AM

Dear Sir / Madam,

Following an awareness campaign originated by [alltrials.net](#), a collaborative organisation, campaigning for proper reporting of all clinical trials, I would like to respectfully urge you to work towards the proposals outlined here: <http://www.alltrials.net/news/patients-and-doctors-campaign-welcomes-plans-to-tackle-unjust-and-dangerous-problem-of-hidden-clinical-trials/> which call for comprehensive registration and reporting of clinical trials.

Thank you for your time, very best wishes, Oliver Jackson, UK.

From: [John C. Markowitz, M.D.](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Wednesday, November 26, 2014 10:52:54 AM

I support your requiring that all funded trials be registered and report results.

John C. Markowitz, M.D.
Research Psychiatrist
New York State Psychiatric Institute
Professor of Clinical Psychiatry
Columbia University College of Physicians & Surgeons
1051 Riverside Drive, Unit #129
New York, NY 10032
(646) 774-8098

From: fess48@verizon.net
To: [clinicaltrials.disseminationpolicy](#)
Subject: support for full and complete disclosure of all data relating to clinical trials to the public
Date: Wednesday, November 26, 2014 11:11:31 AM

Dear NIH:

I support regulations that will prescribe specific procedures for registering clinical trials in the expanded ClinicalTrials.gov registry, and define the information that must be provided. Required information will include descriptive information, recruitment information, location and contact information, and administrative information. The regulations will define additional information needed to comply with specific statutory requirements related to search capabilities, enforcement, posting of both negative results as well as positive results related to trials of drugs and uncleared/unapproved devices, as well as to support efficient entry of valid data, link the trials in the registry database to their results, and to provide a comprehensive registry of clinical trials for the public.

Sincerely,

James Parker
112 Longview Avenue
White Plains, NY 10605

From: [Michael Ashman](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: NIH proposals for transparency in clinical trials
Date: Wednesday, November 26, 2014 11:11:38 AM

Dear NIH

As a public health researcher, a health service worker, and as a user of medicines and medical services I applaud the USA NIH and HHS initiative to make trial registration and publication of results mandatory funding conditions. I utilise a great deal of US research, but would feel more confident in it if it could be demonstrably more transparent. In this matter the interests of global public health and health sciences should over-ride the vested interests of pharmaceutical manufacturers.

With kind regards

Michael Ashman MPH
South Yorkshire, UK

From: [Joy Miller](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All trials
Date: Wednesday, November 26, 2014 11:15:18 AM

It is so important to include all trials to be registered and the results reported otherwise any results are only partially valid.

Jay Millaa

From: [Sam Oddie](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support full release of all clinical trial data
Date: Wednesday, November 26, 2014 11:31:53 AM

Please make this happen now – no other patients should be harmed on account of non disclosure of trial data

Its not hard – lets do it

Sam

Sam Oddie

Consultant Neonatologist | Maternity | Maternity Neonatal Unit

Bradford Teaching Hospitals NHS Foundation Trust

T: 01274 542200 (Switchboard)

<http://www.bradfordhospitals.nhs.uk>

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From: [Robin Winslow](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support you requiring all the trials you fund to be registered and to report results.
Date: Wednesday, November 26, 2014 12:00:47 PM

I support you requiring all the trials you fund to be registered and to report results.

From: [Mohamed Lakhal](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support clinical trials reporting measures in the U.S.
Date: Wednesday, November 26, 2014 12:12:26 PM

I support a rule requiring all the trials funded by the NIH to be registered and to report results.

Sincerely yours,

Dr Lakhal Mohamed ,
Médecin Généraliste, Algérie.

[Envoyé depuis Yahoo Mail pour iPad](#)

From: [Katy Verhelle](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trial reporting measures in the US
Date: Wednesday, November 26, 2014 12:23:45 PM

Dear Sir, Madame,

I support the US Department of Health and Human Services (HHS) and National Institutes of Health (NIH) in proposing to expand requirements to register clinical trials and report results, and to make that a condition of research funding. This is a significant and potentially transformative step in the battle for clinical trial transparency.

Katy Verhelle

Head of Hospital pharmacy

AZ Groeninge Kortrijk

Belgium

From: [Susan Schellenberg](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: National Institutes of Health + clinical trial
Date: Wednesday, November 26, 2014 12:31:16 PM

Dear Sir/Madam

US and Global public health structures and outcomes demand the NIH's undivided approval of the following measures to ensure greater clinical trial transparency.

- register all clinical trials
- report all clinical trial results,
- name the above actions an irrefutable condition of research funding.

Sincerely

Susan Schellenberg
Toronto, Canada M6P 2P4
www.susanschellenberg.com

From: [Robert Newcombe](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Robert Newcombe](#)
Subject: Clinical trial reporting measures in the US
Date: Wednesday, November 26, 2014 1:04:28 PM

Dear Colleagues,

I am writing to express my strong support for the US Department of Health and Human Services and National Institutes of Health proposals to expand requirements to register clinical trials and report results, and to make that a condition of research funding. I agree with the statement by Francis Collins, Director of NIH, that “We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health.” It is extremely important that HHS and NIH don’t water down these strong proposals. I am emailing HHS to say that I support it expanding the law so that more trials have to be registered and reported. I am emailing you to tell you that I support you requiring all the trials you fund to be registered and to report results.

Best wishes.

Robert G. Newcombe PhD CStat FFPH HonMRCR
Professor of Biostatistics
Cochrane Institute of Primary Care and Public Health
School of Medicine
Cardiff University
4th floor, Neuadd Meirionnydd
Heath Park, Cardiff CF14 4YS, UK

Tel: (+44) 29 2068 7260

My book Confidence Intervals for Proportions and Related Measures of Effect Size is now published.

Available at <http://www.crcpress.com/product/isbn/9781439812785>

See <http://www.facebook.com/confidenceintervals>

Home page <https://sites.google.com/site/robertgnewcombe/>

From: [Jeff Rawlings](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Register and report on ALL clinical trials
Date: Wednesday, November 26, 2014 1:41:26 PM

Hello,

I'm writing to express my support for newly proposed changes in regulations on reporting of clinical trials. I strongly believe that every trial funded by our tax dollars be required to report its results. Allowing trials to go unreported can allow biased parties to skew assessments of treatments toward a desired result. This has clearly happened many times, and continues to happen.

This change, and a new transparency, is necessary -- it serves the mission of the NIH and of science in general.

Thanks,
--Jeff Rawlings
Concerned Citizen
Santa Barbara, CA

From: [Breda Cullen](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trials dissemination
Date: Wednesday, November 26, 2014 3:12:13 PM

I fully support your plans to require all the trials you fund to be comprehensively registered and to report their results.

Breda Cullen

From: [Mahon Clare \(RTH\) OUH](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Letter of support
Date: Wednesday, November 26, 2014 3:17:20 PM

Dear NIH,
I am writing to support that all trials funded by NIH be registered and all results should be reported.
Kind regards

Clare Mahon, Lead Therapist (Physiotherapist)
Early Supported Discharge for Stroke, Acute Stroke Unit (Ward 5B), John Radcliffe Hospital, Oxford. OX3
9DU

07717 587631
01865 (5)72723

From: [Sami Hakemian](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All your funded trials should be registered and report ALL results
Date: Wednesday, November 26, 2014 4:38:34 PM

I encourage you to require all the trials you fund to be registered, as well as require each trial to report its results including full data.

From: [Ec Ah](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support reporting results
Date: Wednesday, November 26, 2014 11:58:34 PM

I support NIH requiring all the trials to be registered and to report results.

Gourav Kumar

From: [Peter McCorkell](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials registration
Date: Thursday, November 27, 2014 12:22:00 AM

Hello,

I am an Emergency Physician in New York City and I support the recent proposals to require all NIH trials to be registered and all data released to the public.

Thank you for hearing my input.

-Peter McCorkell, PGY2
New York Medical College
Metropolitan Hospital
Department of Emergency Medicine

From: [denis BOYER](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support clinical trial reporting measures in the US
Date: Thursday, November 27, 2014 2:18:56 AM

Great idea !
I really hope it will occur

Dr denis BOYER
General Practitioner
26120 CHABEUIL
FRANCE

From: [Lucy Edmonds](#)
To: [clinicaltrials.disseminationpolicy](#)
Date: Thursday, November 27, 2014 4:21:55 AM

Dear Sir

I am a UK citizen, supporting the same initiative in the UK, for the transparent registration and full reporting of all results of all clinical trials. I believe strongly that without the publication of all results of clinical trials, true assessment of the value of medical treatments is impossible. The pharmaceutical industry has had plenty of opportunity for self-regulation in this area, and has proven that without legislation this will never happen. The ability to suppress negative or unfavourable results, or simply the full data on interpreted results, is a disservice to the entire population who access medical treatment and a particular insult to those who in good faith agreed to participate in those trials.

Regards
Lucy Samuels

From: [Matthew Thompson](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: NIH clinical trials
Date: Thursday, November 27, 2014 5:33:13 AM

I support you in requiring that all the trials you fund be registered and that the results are reported.

Regards

Matthew Thompson

From: [Ilona Carneiro](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All trial results should be reported
Date: Thursday, November 27, 2014 6:10:48 AM

I support the call for all clinical trials to be registered and their results reported. It is important to have transparency and fairness in medicine. As an epidemiologist, I am committed to providing and sharing evidence. If our evidence is biased, we cannot have a reasonable public health practice.

regards

Dr Ilona Carneiro
Epidemiologist, tutor on MSc in Public Health and author of "Introduction to Epidemiology, 2nd edition"
London School of Hygiene and Tropical Medicine

From: [Riley B](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Increasing regulations and laws to make publishing of ALL trials a reality
Date: Thursday, November 27, 2014 6:38:21 AM

The NIH and HHS must do everything within their power to ensure that registration and publishing of ALL conducted trials becomes a reality in the very near future.

Remember, this affects everyone in the world, the rich cannot escape the lack of knowledge we have because of the shocking lack of competence and ethics displayed by many fields including primarily the pharmaceuticals industry.

If the qualified public can not be allowed to analyse statistical evidence about our drugs, we're all living in a world made more dangerous, unnecessarily.

The history books are riddled with examples wherein the lack of published trial data has resulted in hundreds of thousands of deaths in 1st world countries alone. The actual total in doubtless in the millions.

I urge you, make the right decision, and encourage others to, lest members of my family or yours die a completely avoidable and wasted death in the near or distant future.

Thanks.

Riley

From: fjivins@gmail.com on behalf of [Frank J Ivins](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Trial Reporting
Date: Thursday, November 27, 2014 6:49:27 AM

I'm writing to throw in my support for proposed changes that would require all trials funded by NIH to be registered and to report results. All data is useful and cumulative in our understanding of medical interventions and nothing should ever be left by the roadside simply because it didn't fit in with the pre-conceived hopes of the those conducting the trial. We owe this to ourselves, to our children, and to those who donate their living bodies to furthering our medical understanding.

Thanks you.

Dr. Frank J Ivins

Mobile: 0781 735 2947

From: [Donald MacIntyre](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trial reporting measures
Date: Thursday, November 27, 2014 8:07:41 AM

Dear NIH,

I would like to support this proposal which aims to increase transparency in clinical research.

Best wishes

Donald

Dr Donald MacIntyre
61 High Street
Biggar
ML12 6DA
UK
+44(0)7958 777103

From: [Kim Raper](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registered Clinical Trials
Date: Thursday, November 27, 2014 8:52:51 AM

To whom it may concern

I am concerned about non-registered clinical trials and want you to know that I support your organisation requiring all the trials you fund to be registered and for results to be reported.

This is the ethical approach in a field that is vulnerable to abuse and where the consequences could be catastrophic.

Yours truly

Kim Roper
kimirap65@yahoo.co.uk

From: [Michael West](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials dissemination policy NIH
Date: Thursday, November 27, 2014 9:00:12 AM

Dear Sirs,

I strongly believe that all the trials funded by the NIH should be required to be registered and to report results publicly. This is important for clarity in the scientific process, especially where the work is publicly funded.

Dr. Michael L. West
Division of Nephrology
Department of Medicine
Professor of Medicine
Assistant Dean Research-Clinical Trials
Dalhousie University
Rm 5090 ACC
QE II Health Sciences Centre
5820 University Ave
Halifax NS
Canada B3H 1V8
phone 902 473-4023
fax 902 473-2675
e-mail mlwest@dal.ca

From: [Miro Janosik](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support for registering of trials
Date: Thursday, November 27, 2014 9:29:15 AM

Hello

I just wanted to tell you that I appreciate and support your goal of registering and reporting results of all performed medical trials. It should make medicine better for whole world.

with regards
Miro Janosik, Malacky, Slovak Republic

From: [Sprucebirds](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Research Funding
Date: Thursday, November 27, 2014 10:33:42 AM

We support proposals to expand requirements to register clinical trials and report results. There should be transparency in trials and reporting in everything related to prescription drugs as a matter of public information and safety

Pam and Bill Stevenson
RR#2 Bayfield Ontaraio N0M1G0

From: [Von Delft Tilman \(NHS HIGHLAND\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: registering and reporting trials
Date: Thursday, November 27, 2014 12:17:38 PM

Dear Sir of Madam

I wholeheartedly support support proposals for the NIH to require all clinical trials it funds to be registered and to report results. This is indispensable for the future credibility and accountability of future pharmaceutical trials, for patient safety, and for the reputation of the medical profession.

Regards
Dr Tilman von Delft
General Medical Practitioner
Burnfield Medical Practice
Harris Road
Inverness IV2 4QZ
Scotland

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From: [Jennie Johnson](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Support for more trials to be registered and supported
Date: Thursday, November 27, 2014 12:19:05 PM

It is so important for us all that more trials have to be registered and reported and that this will be a condition of research funding.

Jennie Johnson
Farnham
United Kingdom

From: [Enrique Barros](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: to our health
Date: Thursday, November 27, 2014 2:21:42 PM

I support NIH's effort to promote registration of all trials.
we need this to increase transparency and credibility in science.
congrats,
MD Enrique Barros

From: [Berislav Bulat](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: support to thorough registration of /funded/ trials
Date: Thursday, November 27, 2014 4:07:02 PM

As a medical doctor as well as a private member of interested public, I am all in for making any scientific trials and their results available to the public.

--

Berislav Bulat, MD
Croatia

From: [María Matilde Goodall \(Reyes Bonar\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Funded trials need to be registered and report results
Date: Thursday, November 27, 2014 4:40:53 PM

Dear NIH,

As a medical science researcher, I was taught early on in my career that I have an ethical obligation to only make sure my studies are safe for my participants, but beyond that I have a duty to my participants and funders to use my data and report my results. This gives volunteers the piece of mind that their efforts will benefit if not them then the public at large.

The fact that trials funded by taxpayers dollars do not need to be registered nor report their results undermines the good work of researchers. Please keep volunteers faith in medical research by requiring all trials to register and report their results.

Sincerely,
María Goodall

M. M. Goodall (Reyes Bonar)

From: [Matti](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials
Date: Thursday, November 27, 2014 6:08:52 PM

I support you requiring all the trials you fund to be registered and to report results.

Hooroo Matti

85 Greens Road
Paddington NSW 2021
Australia

From: [John R Jones](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials reporting
Date: Thursday, November 27, 2014 7:16:09 PM

Dear National Institutes of Health,

I support policies to require registration of clinical trials, and reporting of the results. This is both necessary and timely. All interested parties need access to this information.

Sincerely,
John Jones

From: [Aero Ab](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Registering Clinical Trials
Date: Thursday, November 27, 2014 8:27:32 PM

I support NIH requiring all the trials it funds to be registered and to report results.

Thank you,
Shannon Abernathy

From: [Batool](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Friday, November 28, 2014 3:59:28 AM

I do support that trials should be registered and the results should be reported as well. Actually it means good clinical practice.
Batool Rashidi
Sent from my iPhone

From: [Steve Maxwell](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Register all trials
Date: Friday, November 28, 2014 12:54:44 PM

Dear NIH,

Just weighing in, briefly, to urge you to make ALL clinical data available. Please.

Thanks,

Steve Maxwell
Concerned Citizen
602-718-2040

From: [Mike Coleman](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: clinical trial transparency
Date: Friday, November 28, 2014 3:43:49 PM

Dear Sir or Madam,

I am asking you to expand requirements to register clinical trials and report results, and to make that a condition of research funding. This is clinical trial transparency.

Francis Collins, Director of NIH, said, "We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health."

Please don't water down these strong proposals.

Yours sincerely,

Mike Coleman.

From: [Simon Beecroft](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Transparency in clinical trials reporting
Date: Friday, November 28, 2014 3:55:15 PM

To whom it may concern,

I am medical student studying at the University of Manchester in the UK and I am strongly in favour of robust regulation on clinical trials reporting. A number of studies have shown that there is systematic publication bias within the medical literature despite repeated attempts to provide guidance or incentives to prevent it. As a significant funder of medical research, the NIH has a duty to ensure that all trials funded in any part by public money report their outcomes in a timely manner and make results available for scrutiny by academics, healthcare professionals and the general public. Selective reporting of clinical trials harms patients; this should be all the knowledge required to make a decision in this area. Do the right thing and put people first.

Kind regards,
Simon Beecroft

From: [Michael Montani](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: I support NIH requiring all the trials it funds to be registered and to report results.
Date: Friday, November 28, 2014 5:36:49 PM

I support NIH requiring all the trials it funds to be registered and to report results.

--

Michael Francis Montani
630.740.5713
michaelmontani@gmail.com

From: [Adam Kimble](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials Dissemination Policy Proposal
Date: Saturday, November 29, 2014 1:36:04 AM

I support the proposed requirement that all trials you fund must be registered and results reported.

Sincerely,

Mr. Adam Kimble
1154 Olde Cameron Lane
Franklin TN 37067

From: [Kara Bagnall](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Proposal support
Date: Saturday, November 29, 2014 10:29:06 AM

I support your proposal to require all research you fund to be registered and all results to be reported.

Regards

Kara

Kara Bagnall

From: [D. E. Packham](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Saturday, November 29, 2014 12:28:32 PM

Dear Sir/Madam,

It is essential that all clinical trials are registered and their results fully and openly reported. This is the only way to restore confidence in this area.

Yours faithfully,

D. E. Packham

Materials Research Centre,
University of Bath.

From: Stephen Halpin <stephenjhalpin@gmail.com>
Sent: Saturday, November 29, 2014 1:02 PM
To: clinicaltrials.disseminationpolicy
Subject: Clinical trial reporting

Dear NIH,

I am a medical doctor working in the UK NHS and I am writing to contribute to the consultation regarding proposals to expand requirements to register clinical trials supported by the NIH and ensure results are reported.

I strongly support the proposal that results of all trials must be reported, and that NIH funding should be granted with the guarantee that this would happen.

I think that without full and transparent reporting of all trials clinicians cannot make fully informed decisions for our patients.

Yours faithfully,

Dr Stephen Halpin
Leeds, UK

From: robin holtedahl <robi-hol@online.no>
Sent: Sunday, November 30, 2014 4:24 AM
To: clinicaltrials.disseminationpolicy
Subject: Transparency clinical trials

I fully support the NIH requiring all the trials it funds to be registered and to report results.
Yours sincerely
Robin Holtedahl, MD, Oslo, Norway

--

Sendt med Operas e-postklient: <http://www.opera.com/mail/>

From: Felix B. <felixab1988@gmail.com>
Sent: Sunday, November 30, 2014 10:40 AM
To: clinicaltrials.disseminationpolicy
Subject: Improvement of clinical trial transparency

Dear Madam of Sir,

I am writing you in context with the AllTrials-Campaign and was glad to read, that you made proposals about registering and reporting of clinical studies you fund. This is a huge step in the right direction to make these studies available for everyone! Keep it up!

Sincerely,
Felix A. Bauer (Germany)

From: Hans C Ossebaard <hcossebaard@gmail.com>
Sent: Sunday, November 30, 2014 10:51 AM
To: clinicaltrials.disseminationpolicy
Subject: transparency and quality in health care research

Follow Up Flag: Follow up
Flag Status: Flagged

L.S.,

The US Department of Health and Human Services (HHS) and National Institutes of Health (NIH) have announced proposals to expand requirements to register clinical trials and report results, and to make that a condition of research funding. This is a GREAT step in the battle for clinical trial transparency, both nationally and globally.

Me and many colleagues, support the NIH in requiring all the trials it funds to be registered and to report results transparently in the name of continuous health care quality improvement.

1.

dr Hans C. Ossebaard

From: Alberto González y Garcia <ali.gonzalez@ziggo.nl>
Sent: Sunday, November 30, 2014 11:00 AM
To: clinicaltrials.disseminationpolicy
Subject: Mail showing Support for registration and reporting of trials and funding

Greetings,

I would like to show my support for requiring that all trials that you fund to be registered and to report results.

From: BRIAN ANDREWS <brianandr@gmail.com>
Sent: Sunday, November 30, 2014 11:00 AM
To: clinicaltrials.disseminationpolicy
Subject: SUPPORT

I support FULL disclosure of all clinical trials. I believe all trials should be made available for peer review, without any legal limitation. I also believe full reporting of clinical trials should be retrospective. Furthermore I believe all governments should preclude the import or sale, within their jurisdiction, of any drug or therapy for which FULL disclosure of ALL trials has not been made.

How else can a medical professional fully judge the suitability of a medication or treatment for any patient?

Yours sincerely,

Brian Andrews.

United Kingdom
brianandr@gmail.com

From: William Graham <will.graham@talktalk.net>
Sent: Sunday, November 30, 2014 11:17 AM
To: clinicaltrials.disseminationpolicy
Subject: trial registration policy

Dear NIH

I'm strongly in favour of the proposal that any trial you fund should be registered, and openly reported. Although I'm not a US resident, I'm commenting because this is an issue that affects patients worldwide.

Yours faithfully

Will Graham

From: David O'Reilly <dave@breakdesign.com>
Sent: Sunday, November 30, 2014 1:14 PM
To: clinicaltrials.disseminationpolicy
Subject: Support for the requirement to register funded clinical trials

Good day

I would like to express my support for the requirement to register all the clinical trials funded by NIH and for the results to be reported.

Best regards

David O'Reilly

From: Liz Waller <lizwaller@gmail.com>
Sent: Sunday, November 30, 2014 3:13 PM
To: clinicaltrials.disseminationpolicy

Dear NIH,

I would like to make you aware that I support the NIH requiring all the trials it funds to be registered and to report results.

This is particularly important to me as I have a rare condition that will mean I die in a couple of years, next month is my 40th birthday so I'm not very old. Unfortunately because I have a rare cancer form, it doesn't receive much funding and it's also a form of cancer that's heterogeneous so there's even less attention on finding a solution for it. People like me with rare conditions may be most likely to benefit from cross sharing of knowledge, even knowledge that's arises during investigation of different conditions, than research dedicated to the precise oligodendroglioma brain tumour that I have. Regarding the small pockets of research happening in different geographical locations into my condition, it's so important for clinical developments and knowledge to be shared so best use of research budgets is guaranteed. Otherwise time will be wasted with duplication and other pointless exercises. Brain tumours are the form of cancer to which the most years of life are lost (they affect the young), the flip side is that breakthroughs could return many years of life to sufferers.

Many thanks for your kind consideration.

Liz Waller

From: Peter Dam <peter.c.dam@gmail.com>
Sent: Monday, December 01, 2014 5:29 AM
To: clinicaltrials.disseminationpolicy
Subject: Registration of trials

Dear Madam/Sir,

I strongly support full registration of all clinical trials plus reporting of all results.
I am in full agreement with your director Francis Collins, who said, "We owe it to every participant and the public at large to support the maximal use of this knowledge for the greatest benefit to human health."

Thank you very much for your consideration.

Best regards,

Peter Dam

From: oliver2@aol.com
Sent: Monday, December 01, 2014 8:01 PM
To: clinicaltrials.disseminationpolicy
Subject: please expand clinical trials registration and disclosure requirements

To whom it may concern:

I want to add my enthusiastic support for requiring all human subjects trials to be preregistered and all data made publicly available to follow through on our commitment to human subjects who participate in such trials. Anything less would be fraud because we promise human subjects that their data will help other human beings. If the data are buried without publication, we have failed them.

cordially,

David

David Antonuccio, Ph.D.
Diplomate in Clinical Psychology, ABPP
Professor Emeritus of Psychiatry and Behavioral Sciences
University of Nevada School of Medicine
401 W. 2nd St., Suite 216
Reno, NV 89503
775-682-8439
fax 775-327-5218
email: dantonuccio@medicine.nevada.edu

Private Practice
3732 Lakeside Dr., #200
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775-329-3393 or 775-826-6218
FAX 775-827-4799
email: oliver2@aol.com

Author of Butt Out: A Compassionate Guide to Helping Yourself Quit Smoking, With or Without a Partner
<http://www.smashwords.com/books/view/270542>
<http://www.barnesandnoble.com/w/butt-out-david-antonuccio/1114057123>
<http://www.amazon.com/Butt-Out-Smokers-Book-ebook/dp/B00AWELY2C>

From: Ainley Wade <ainley.wade@easynet.co.uk>
Sent: Tuesday, December 02, 2014 10:01 AM
To: clinicaltrials.disseminationpolicy
Subject: All Trials reporting

I would like to support the proposal that all publicly funded clinical research and trials should be registered and the outcomes published to inform choice for the prescriber and patient.

I was annoyed last year to realise what a high proportion of trials were never reported because the sponsors did not like the results. Now retired, I spent my working life compiling, checking and editing pharmaceutical reference books such as 'Martindale: The Extra Pharmacopoeia' and the 'British National Formulary' . It's galling to realise how misled we were by the lack of information on negative trials.

I hope your proposals will help transparency and produce a better -balanced view of the worth of medicines.

Ainley Wade
Bath, England

From: Avey, Marc <mavey@ohri.ca>
Sent: Tuesday, December 02, 2014 2:14 PM
To: clinicaltrials.disseminationpolicy
Subject: Trial Registration and Reporting

To whom it may concern,

I am writing in support of the NIH requiring that all trials which it funds to be both Registered and that all results be reported within a set timeframe (delayed reporting of results is equally pernicious to non-reporting of results).

I would further suggest that the NIH consider exploring the requirement for preclinical in vivo animal studies for both registration and reporting of results. The arguments for the registration and required reporting of preclinical in vivo animal studies is similar to those of human clinical trials. The registration could be (initially) limited to translational studies of efficacy and toxicity (safety) studies as these more closely resemble human clinical trials. The United States already has an excellent resource for registering clinical trials (clinicaltrials.gov) in humans which could easily be adapted to preclinical in vivo animal studies. Indeed, combined trials using humans and mice can readily be found on clinicaltrials.gov already (e.g. NCT00177099). I have attached a one page summary outline why registration of preclinical animal studies is any important further step forward the NIH should consider.

Sincerely,

Marc

Marc T. Avey, PhD
CIHR Postdoctoral Fellow
Ottawa Hospital Research Institute
Center for Practice Changing Research Building
The Ottawa Hospital - General Campus
501 Smyth Road / PO Box 201B / Ottawa / Ontario / Canada / K1H 8L6
Email: mavey@ohri.ca
Phone: 613-737-8899 ext: 73923
Fax: 613-739-6938



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de la Protection des renseignements personnels (info.privee@hopitalottawa.on.ca), puis effacez le courriel ainsi que les pi?ces jointes et toute autre copie. Merci.

From: Pascal Geldsetzer <pgeldsetzer@gmail.com>
Sent: Tuesday, December 02, 2014 9:43 PM
To: clinicaltrials.disseminationpolicy
Subject: Support for requiring the registration and full results reporting of trials

Dear Sir or Madam,

I'm writing to voice my support for the proposal to make it a requirement for all trials funded by the NIH to register and fully report their results.

Best,
Pascal

From: Marco Setiawan <marcosetiawan@yahoo.com>
Sent: Wednesday, December 03, 2014 8:33 AM
To: clinicaltrials.disseminationpolicy
Subject: Report the results of all clinical trials

Dear NIH,

I support your proposal to require all clinical trials that receive funding from the National Institutes of Health (NIH) to be registered and produce a detailed report of the trials' results.

Kind regards

Marco Setiawan

From: Joshua Goodwin <jd-goodwin@Dal.Ca>
Sent: Wednesday, December 03, 2014 10:33 PM
To: clinicaltrials.disseminationpolicy
Subject: Proposal Response

To whom it may concern:

We are writing to inform the NIH we support it requiring that the clinical trials it funds be registered and their results reported.

Sincerely,
Joshua Goodwin
VP Communications
Dalhousie University Student AllTrials Society
Dalhousie University
Halifax, NS, Canada B3H 4R2

From: chriswicks1@gmail.com on behalf of Chris Wicks <two@chriswicks.com>
Sent: Friday, December 05, 2014 3:37 AM
To: clinicaltrials.disseminationpolicy
Subject: Comment on Clinical Trials Policy

Dear Sir / Madam,

I wholeheartedly support your proposal to expand reporting of clinical trial results, and to make that a condition of research funding.

Around half of all clinical trials for treatments we use today have never published results and thousands have never even been registered. Information on what was done and what was found in these trials could be lost forever to doctors and researchers, leading to bad treatment decisions, missed opportunities for good medicine, and trials being repeated. Hundreds of thousands of patients took part in those trials in the expectation that their results would be used by doctors and researchers to improve understanding of disease and the development of new treatments.

NIH is in a strong position to shift the cultural norms around this dangerous practice, and other funders should follow their lead. Please don't be pressured into watering down these proposals.

Yours sincerely,
Chris Wicks

From: Nichols, Linda O. <Linda.Nichols@va.gov>
Sent: Friday, December 05, 2014 12:57 PM
To: clinicaltrials.disseminationpolicy
Subject: Proposed NIH policy on reporting to clinical trials.gov

I think it is an excellent idea to have all trials reported to clinicaltrials.gov. We always do ours there but the guidelines are very specific and the new proposed rulemaking seems to follow those guidelines, also. For trials that have qualitative components or outcomes or do not fit the model of drug trials, the options available are very limited. We have had detailed discussions with the clinicaltrials staff to help work through how to report outcomes. We have gotten results posted but they do not necessarily reflect the findings of the study that we would like to have available.

Linda

Linda O. Nichols, PhD.
Co-Director, Caregiver Center
VA Medical Center Memphis
Professor, Preventive and Internal Medicine
University of Tennessee Health Science Center
1030 Jefferson Avenue (11h)
Memphis, TN 38104
(901) 523-8990, press 1, then ext. 5082
(901) 577-7439 (fax)

What do we live for, if it is not to make life less difficult to each other? George Eliot

From: Rosalind Revans [um12rr] <um12rr@leeds.ac.uk>
Sent: Saturday, December 06, 2014 10:13 AM
To: clinicaltrials.disseminationpolicy
Subject: Clinical trials policy

Hi

I would like to add my voice to the many supporting increased registration and result reporting following clinical trials. This is vitally important to allow doctors to make good, evidence based decisions and to get the most from all the money spent on healthcare research.

I would also like to add that making maximal use of data and making sure that data collected is published in some way shows respect for the patients that have participated in this trial normally in a way that increases risk in their lives.

Please respect research participants

Rosalind Revans

Sent from Windows Mail

From: Derek P. Bumgardner <derekpb.1097@gmail.com>
Sent: Saturday, December 06, 2014 2:59 PM
To: clinicaltrials.disseminationpolicy
Subject: Transparency in clinical trials

I strongly encourage complete transparency for the results of all clinical trials within the United States to be published regardless of outcome with any associated information about the trial relevant to research and physician decision making.

This is not an academic exercise. Patients and physicians need all information associated with an intervention for shared-decision making. If this information is unpublished, not only is it difficult to make clinical decisions, but it causes potential unknown harm to patients.

We cannot as an ethical society permit clinical interventions to be performed without all the information.

From: Cian O' Mahony <cian.omahony@cremeglobal.com>
Sent: Thursday, December 11, 2014 4:55 AM
To: clinicaltrials.disseminationpolicy
Subject: Support for clinical trial reporting measures in the US

Hi,

I support NIH requiring all the trials it funds to be registered and to report results.

Cian.

Cian O'Mahony *Head of Expert Modelling and Statistics*

p: +353 1 677 0071 | e: cian.omahony@cremeglobal.com | w: cremeglobal.com |
Trinity Technology and Enterprise Campus, Grand Canal Quay, Dublin 2, Ireland

Meet us at:

Society for Risk Analysis (SRA) 2014 Annual Meeting, Denver, CO 7-10 December 2014
ILSI North America Annual Meeting, Phoenix, AZ, 16-21 January 2015

[View our presentations from past events \(link\)](#)

From: j.k. lipka <bebertsmama@gmail.com>
Sent: Saturday, December 13, 2014 6:01 AM
To: clinicaltrials.disseminationpolicy
Subject: I support the registry of all clinical trials

I am a physician and I believe it is to the benefit of my patients, the public, and myself to have greater transparency in the realm of medical and pharmacologic research. All trials should be registered and the public should have access to them existing, regardless of outcomes. To have only "positive" results reported impedes good medical decision making.

I support the new rule regarding registration of clinical trials and making that information accessible to the public (the HHS proposal to expand the scope of the 2007 FDA Amendment Act).

Thank you,

Jennifer Lipka, D.O.
106 Houndstooth Way Apt. 101
Hollidaysburg, PA 16648

From: Joe Holmes <j.holmes72@hotmail.co.uk>
Sent: Sunday, December 14, 2014 2:37 PM
To: clinicaltrials.disseminationpolicy
Subject: Clinical Trial Reporting

I am emailing to show my support for expanding the requirements for registering and reporting on clinical trials.

ALL clinical drug trials should be registered. ALL findings should be reported in a timely manner. ALL results should be made publicly available. NOTHING should slip through the net for the sake of providing the best medical care possible based on the fullest possible picture of the science for any clinical treatment.

Thank you

Joe Holmes

From: Martin Bobrow <mb238@cam.ac.uk>
Sent: Friday, December 19, 2014 4:27 AM
To: clinicaltrials.disseminationpolicy
Subject: clinical trial reporting measures

I strongly support NIH requiring all the trials it funds to be registered, and to report results. The blatant manipulation of the statistics of drug trials, in both private and publicly funded domains, has been a blot on the name of clinical science for decades. It has also been a huge disservice to public health, adding needlessly to drug costs and complexity for prescribers.

Please keep these proposals strong and clear and simple, resist the inevitable pressures from interested parties to water it down.

Thank you for showing the world that this abuse can be tackled

Martin Bobrow

From: Shanahan, Daniel, BioMed Central Ltd. <Daniel.Shanahan@biomedcentral.com>
Sent: Friday, December 19, 2014 9:31 AM
To: clinicaltrials.disseminationpolicy
Subject: NIH Clinical Trials Dissemination Policy

To Whom It May Concern,

I am writing to express my support for your requiring all clinical trials that are funded through the NIH to be registered with a primary registry, as defined by the World Health Organisation (<http://www.who.int/ictrp/network/primary/en/>), and all results reported in an honest and transparent manner, without selective publication of outcomes or analyses, in a publically-accessible location.

Regards,

Daniel Shanahan
Associate Publisher

BioMed Central

236 Gray's Inn Road | London WC1X 8HB | United Kingdom

Tel +44 (0)20 7562 2943

Mob +44 (0)7787 299145

daniel.shanahan@biomedcentral.com

www.biomedcentral.com

From: Stephen Adams <stevenad@mail.ubc.ca>
Sent: Friday, December 19, 2014 4:34 PM
To: clinicaltrials.disseminationpolicy
Subject: clinical trial posted results

I do systematic reviews on the statin drugs for the Heart Group in the Cochrane Database of Systematic Review. I work at the University of British Columbia in Canada.

I support you in requiring all the funded trials to be registered and to report results.

With Kind Regards

Stephen Adams

From: Kristina Campbell <bykriscampbell@gmail.com>
Sent: Saturday, December 20, 2014 1:09 PM
To: clinicaltrials.disseminationpolicy
Subject: Registration of all trials

Dear NIH:

I am a science writer who speaks with scientists around the world on a daily basis.

I support the requirement of all the trials you fund to be registered and for researchers to report results. This is an important step in responsible science, and will restore some of the credibility of US research in the eyes of international colleagues.

Best,
Kristina Campbell
Victoria, BC, Canada

--

Find me on Twitter: @bykriscampbell

From: Nick Kerrison <nickkerrison@gmail.com>
Sent: Sunday, December 21, 2014 10:30 AM
To: clinicaltrials.disseminationpolicy
Subject: Trial R&R proposal support

I am writing to tell you that i support your proposal to make registration and reporting in clinical trials a requirement of funding. I think that clinical trial transparency is the biggest issue in science right now and it's essential to get it right to improve science and medicine globally, right now and in the future. I think that registration and reporting of results are sensible requirements for funding because we can't allow trials to go unregistered or unreported any longer.

Thank you for reading,

Nick Kerrison

Undergraduate statistics student

From: Andrew Markos <andrew.markos@hotmail.co.uk>
Sent: Sunday, December 21, 2014 12:36 PM
To: clinicaltrials.disseminationpolicy
Subject: Showing support for decision to require all the trials you fund to be registered and their results reported.

I am sending this email to show my support for your decision to require all the trials that you fund to be registered and for their results to be reported.

Andrew Markos
21 Frederick Road
Selly Oak
Birmingham
B29 6NX
United Kingdom

From: alex <space_monkey_tuesday@hotmail.com>
Sent: Monday, December 22, 2014 6:01 AM
To: clinicaltrials.disseminationpolicy
Subject: in support of requiring all trials to be registered and results to be reported

Hi,

My name is Alexander Kurth.

I am writing a quite letter in support of the proposed new policy that would require all trials funded by the NIH to be registered, and results of these trials to be publicly reported.

This will promote transparency and increase the availability of data for further scientific data, and prevent the suppression of valuable data that may disagree with the "intended" results of the trials.

I thank you for your time.

Sincerely,

Alexander Kurth.

From: Olaf Koort <olaf.koort@gmail.com>
Sent: Monday, December 22, 2014 9:37 AM
To: clinicaltrials.disseminationpolicy
Subject: Registration of clinical trials and reporting of results

To whom it may concern,

I am writing to you regarding a matter of importance for people everywhere, considering the eminence of the US in the field of medical research, and the global reach this research and the resulting treatments will have.

As I understand it, the NIH is considering measures to increase clinical transparency by requiring all the trials it funds to be registered and to report their results.

Since medical trials are necessary to develop effective treatments with fewer and better understood side effects, full disclosure of the results of those trials, whether they be positive or negative, is therefore of the utmost importance for developing effective and safe treatments.

In short, lives are at stake and I believe that the introduction these requirements as a condition for you funding will help save more than a few.

Yours faithfully,

Olaf Koort

From: jfrangio@bidmc.harvard.edu
Sent: Tuesday, December 23, 2014 9:28 PM
To: clinicaltrials.disseminationpolicy
Subject: Comment on Proposed NPRM and NIH Policies

Dear Sir or Madam,

I respectfully disagree wholeheartedly with the proposed NPRM and NIH policies on Clinical Trial Results.

As a Professor of Medicine and Professor of Radiology at Harvard Medical School, I can say without reservation that even the existing policies regarding clinicaltrials.gov registration and data submission are overly burdensome, expensive, and difficult to comply with. The proposed two new policies to expand requirements and increase this burden are unacceptable.

Our experience is that at least a full-time administrator is required to maintain registration and record upload for even a small clinical trial of 50 patients. It is unclear what, if any, benefit anyone derives from all of this effort. It is unlikely to impact enrollment, because most academic studies are drawing off a local patient base and are highly specialized. It's not going to impact the science, because if the trial's results are important then there is incentive to publish them quickly and if the trial invalidates a hypothesis then the physician-scientists will be revising the hypothesis and opening a new trial. All it does is increase work for everyone and slows overall progress considerably.

I am in the process of transitioning to a small business, and there too, this policy will only increase costs, disincentivize us to move devices and drugs into clinical trials, and/or delay progress.

Draconian reporting requirements are not productive. In fact, the NIH and FDA should consider relaxing requirements until Phase 3 rather than slowing progress before then. I know of no data that suggest the current policy, or the proposed policies, will have a significant impact on human health. And, from my personal experience, I believe that they do quite the opposite.

Sincerely,

John V. Frangioni, M.D., Ph.D.
Harvard Medical School

John V. Frangioni, M.D., Ph.D.

<http://www.centerformolecularimaging.org/>

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From: John <chamberlayne@lineone.net>
Sent: Sunday, January 04, 2015 11:48 AM
To: clinicaltrials.disseminationpolicy
Subject: NIH consultation on trial reporting

The British Porphyria Association considers that it is important that all trials that you fund should be registered, and full results should be reported.

We represent patients with rare diseases. As such, results need to be combined across many countries, to gather sufficient numbers for reliable results.

John Chamberlayne
BPA Chair



The British Porphyria Association

Registered Charity No. 1089609

136 Devonshire Road

Durham City

DH1 2BL

www.porphyrria.org.uk

Helpline: 0300 30 200 30

From: D.V.Moseley <mosd@bluebottle.com>
Sent: Friday, January 09, 2015 11:18 AM
To: clinicaltrials.disseminationpolicy
Subject: Proposed expanded reporting of clinical trial results

I strongly welcome these proposals and hope that they will end the practice of failing to report adequately on adverse events in patients, especially in those withdrawn from trials. The proposals in (1)(ii) and (3)(ii)(C) of para 11.48(a) are helpful.

From: Peter Edwards <alltrials@peteredwards.me.uk>
Sent: Friday, January 09, 2015 1:27 PM
To: clinicaltrials.disseminationpolicy
Subject: Registration and Reporting of Clinical Trials

I fully support your proposal to insist that all trials are registered, and that all results are published, and that these requirements should be conditions of receiving funding.

Peter N Edwards
20 Riselaw Terrace
Edinburgh
EH10 6HW
Scotland, UK

From: JOSE IGNACIO PIJOAN ZUBIZARRETA
<JOSEIGNACIO.PIJOANZUBIZARRETA@osakidetza.net>
Sent: Tuesday, January 13, 2015 2:12 AM
To: clinicaltrials.disseminationpolicy
Subject: endorsement of AllTrials Campaign

Dear Sir/Madam,

As a clinical epidemiologist and researcher, that gives support to the design, conduct, analysis and diffusion of non-commercial clinical trials and other clinical research, I would like to show my strong support to the new policies your organization is implementing with a focus on improvement in total transparency in all phases of clinical research, from the rationale and main design features of studies, proper trial registration, clear description of scientific and logistical procedures used to fair presentation of results in scientific forums, mainly peer-reviewed journals, following internationally agreed guidance on the ways methods and results should be published (e.g. CONSORT set of guidelines).

I am also definitely in favor of this being a requirement for funding of research projects by public agencies and organizations.

I would be willing to participate in collaborative initiatives aimed at achieving this important target.

Yours, sincerely

Jose Ignacio Pijoán Zubizarreta

Jefe de Sección-Unidad de Investigación-Hospital Universitario Cruces
Unidad de Epidemiología Clínica y Soporte Metodológico
BioCruces Health Research Institute
UICEC de BioCruces-SCReN (Spanish Clinical Research Network)
CIBERESP (CIBER de Epidemiología y Salud Pública)

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correo electrónico: joseignacio.pijoanzubizarreta@osakidetza.net

From: jenny kirk <jennykirk15@gmail.com>
Sent: Thursday, January 15, 2015 8:47 AM
To: clinicaltrials.disseminationpolicy
Subject: funding clinical trials

Your proposals to expand requirements to register clinical trials and report results, and to make that a condition of research funding is a significant and potentially transformative step in the battle for clinical trial transparency. I support your requiring all the trials you fund to be registered and to report results.

From: Carla Greenbaum <cjgreen@benaroyaresearch.org>
Sent: Monday, January 26, 2015 5:09 PM
To: clinicaltrials.disseminationpolicy
Subject: Draft NIH policy

I read the special report of draft NIH policy on US Clinical Trial Registration and Results Submission with great interest.

I disagree, not with the concept of assuring that clinical trial information is reported regardless of whether the results are positive or negative, but with the execution of the concept.

Considerations:

1. One purpose of these rules is to assure dissemination of what clinical trials are available to subjects.
 - a. While, theoretically, listings on clinicaltrials.gov could enable subjects to find applicable trials, in reality this website is currently markedly unfriendly to potential participants. The terminology is difficult, the search engines at times faulty, and the results often out of date. Thus instead of being beneficial, this website is often harmful and frustrating to patients.
 - b. The proposed rules increasing the number and types of trials on clinicaltrials.gov will only make this problem worse for potential subjects. Many of these other types of studies do not need to recruit subjects; thus, the subject is misled and investigators will have an additional burden explaining this situation.
2. Impact on communication to subjects
 - a. Once a trial is listed on clinicaltrials.gov, the required wording for consent forms is poorly phrased and detracts from assuring potential participants understand and consent for a study. Why this should be a required part of the consent is unclear. If anything is required, just a statement that they can find more information on clinicaltrials.gov should be sufficient.
3. Another purpose of the rules is to assure that all results are available regardless of outcome. The problem here again is execution.
 - a. In an attempt to make reporting “standard”, there is little useful information conveyed regarding results. The sophisticated user would need more information, and the unsophisticated user would not be able to place results in context. Before broadening the mandate, it would be useful to know who has actually used data and for what purpose.
 - b. In addition to being of limited utility and potentially misleading, putting data in such format is essentially an unfunded mandate.
 - c. Broadening the scope of studies that would need to be included would make the “standard” format potentially even less informative.

My thoughts are that rule-makers should take a big step back and look at the big picture question of what is trying to be accomplished. Informing patients about potential trials is a great aim – this system does this extremely poorly. Another aim is to assure participants know about results of studies. This could be better accomplished by asking IRB's to request a data dissemination plan to participants (i.e. what will you tell them and when?)

The conclusion of Figure 1 in the special report is that if you make a rule, most people follow it. Figure 2 shows that about 1/3 of completed trials have posted results. A better figure might be how many of these that posted results have had the information available elsewhere? Another important outcome, as alluded to above, is who actually accessed the data on these studies, and what did they learn or do with this information?

In other words, bring a scientific skepticism to the purported benefits and more systematic attention to the risks (frustrations, delays, costs) of rules, just like all clinical trialists must do in our work.

Thank you for the opportunity to comment.

Sincerely,

Carla Greenbaum MD
Director, Diabetes Program
Benaroya Research Institute
1201 9th Ave
Seattle, WA 98101 206-342-
6933

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From: [Aino Kumpare](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical trials
Date: Tuesday, January 27, 2015 3:16:52 AM

Dear Sir/Madam,

I support the NIH proposal to make registration and reporting a condition of funding.

If action is not taken urgently, information about thousands of clinical trials and medicines we use everyday could be lost forever, leading to bad treatment decisions, missed opportunities for good medicine, and trials being repeated unnecessarily.

Regards,
Aino Kumpare

From: Karen Purdom <kpurdom@clear.net>
Sent: Wednesday, February 04, 2015 3:49 PM
To: clinicaltrials.disseminationpolicy
Subject: Public Comment

To whom it may concern on proposed rules for clinical trials,
I find it very frustrating that 99% of the time when I view completed studies there are no results posted. Additionally if there are results available in peer to peer journals of varying specialties one has to have a subscription to access the article and if one doesn't it is usually available for a one time fee per article around \$35. Since these trials are funded by the NIH access by citizens should be free. Furthermore, it should be mandatory for all recipients of any government funds to post results when the trial stops no matter what phase that happens to be, and why if it ends early; along with findings up to that point. As someone who lives in a rural area that will not be able to participate in any clinical trials, if there is something that is shown to have desirable results; I could theoretically take the information to my healthcare provider and replicate the study. Thank you for your consideration.

Sincerely,
Karen Purdom

From: Oliveto, Alison <OlivetoAlison@uams.edu>
Sent: Friday, February 06, 2015 11:50 AM
To: clinicaltrials.disseminationpolicy
Subject: Draft NIH Policy Comments

Good morning!

I have a few comments to share regarding this draft policy:

1. This policy seems more stringent than the current FDA laws. Given the ever increasing administrative burden on researchers, please reconsider having more stringent requirements.
2. This policy does not reward investigators who do publish results within 12 months of completing the trial as it appears that they will still have to comply with results reporting. If the issue is delays in publishing, wouldn't the goal be to increase the speed with which results are published? So for those findings that are in press or published, can the investigator upload the citation or a copy of the PCMIID manuscript? This might reinforce speedier publication of findings without creating more research burden.
3. The clinicaltrials.gov system is extremely inflexible and not user-friendly, having been set up more for clinical trials involving drugs/biologics and the "one size fits all" approach creates difficulties with registration and results reporting. This again create undo burden as well as sets up a scenario that, for instance, results reported in the way the clinical trials.gov system allows doesn't capture the actual data or the "whole picture." Analyses that are used for certain trials cannot be entered, so investigators often need to spend time that is not value-added to getting the manuscript published in order to have the results reported in a manner the the software will accept. Health services researchers have difficulty registering their trial. Basic human studies researchers who have subjects blinded to the actual drugs under study need to set up the trial in a way that doesn't break the blind and cannot report results until all such studies have been completed. Thus, before NIH moves forward, a careful consideration of how the system can be modified to allow for different types of studies and results reporting.
4. How will compliance be monitored? Given the scarcity funding climate, will dollars be moved from funding grants to policing this policy?

Please let me know if you would like further clarification or discussion.

Thank you for your time.

Kind regards,

Alison

Alison Oliveto, Ph.D.
Team Leader, Methods and Processes Group
Translational Research Institute
Professor and Vice Chair for Research
Department of Psychiatry and Behavioral Sciences
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From: [Rich](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: All clinical trials to be registered and reported
Date: Tuesday, February 10, 2015 1:16:36 AM

To whom it may concern,

If you run the same clinical trial twice, even a completely balanced one the results will be different. If we allow people to only publish one of these trials then we get a biased view of the data. The only way to be able to test whether something works is to include all the data. This is why I support you requiring all trials that you fund being registered and the results reported.

Regards,
Richard

From: [Laakso, Joseph](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Endocrine Society Comments on Notice Number NOT-OD-15-019
Date: Tuesday, February 10, 2015 1:38:43 PM
Attachments: [es_signature_logo22720c9](#)
[Endocrine Society Letter to NIH on Clinical Trials NPRM and Policy.pdf](#)

To Whom it May Concern:

Please see the attached letter to Acting Director Sarah Carr from Dr. Richard J. Santen, Endocrine Society President.

Thank you,
Joe Laakso



JOSEPH M. LAAKSO, PHD ASSOCIATE DIRECTOR, SCIENCE POLICY

2055 L STREET NW, SUITE 600, WASHINGTON, DC 20036

T. 202.971.3636 F. 202.736.9705 D. 202.971.3632

jlaakso@endocrine.org endocrine.org



Acting Director Sarah Carr
Office of Clinical Research and Bioethics Policy, Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Acting Director Carr,

The Endocrine Society appreciates the opportunity to provide comments on the draft policy on Dissemination of NIH-Funded Clinical Trial Information, and also to the Notice of Proposed Rulemaking (NPRM) for Clinical Trials Registration and Results Submission under Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Endocrine Society's membership of over 18,000 includes many clinical researchers who conduct clinical trials with the participation of human subjects. We support the intention of the NPRM and draft policy to improve the management and utilization of data from clinical trials sponsored by the National Institutes of Health (NIH); however we have several concerns that we urge the NIH to address prior to the release of the final policy.

Endocrine Society researchers report that submitting results to clinicaltrials.gov is a tedious and complicated process. For example, form fields and checklists require the completion of items that do not apply unambiguously to the investigator's specific study, suggesting that the processes on clinicaltrials.gov may not be readily tailored to each specific investigator. Additionally, the administrative burden placed on clinical researchers in order to implement the draft policy activities would require a significant percent effort allocation which is currently neither accommodated by current grant budget structure nor necessarily in accordance with university policy regarding effort requirements. Furthermore, the draft policy activities may be redundant to current processes; for example, published manuscripts that include the required information could be submitted directly to clinicaltrials.gov without having to re-enter these data element into form fields. **We therefore strongly urge the NIH to make clinicaltrials.gov a more user-friendly experience through solicitation of specific feedback from users of the website and the development of more streamlined processes.**

The Endocrine Society appreciates and supports NIH efforts to require the submission of negative results so that they can contribute to our understanding of drug efficacy and underlying physiology. We are concerned, however, that the draft policy does not include explicit data curation standards and policies to ensure that research results are robust and reproducible. Specifically, the inclusion of unpublished research results may introduce data that have not been subject to strict peer-review. Additionally, the NIH should provide oversight to ensure that end users of the data are responsible parties that can appropriately interpret the data. **We therefore recommend that the final policy incorporate guidelines for data curation and content management, such as peer review for unpublished results as a requirement for the inclusion of data in clinicaltrials.gov.**

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Finally, **the Endocrine Society recommends that the final policy include the following considerations to ensure that investigators are given sufficient time to submit results:**

1. A provision should be added to defer submission for investigators with manuscripts under review for the study in question, so that the publication can be released prior to posting results on clinicaltrials.gov.
2. A more thoughtful approach should be given to the definition of the end of a study. As we understand the NPRM, the end of a study is defined as the last clinical intervention. However, this definition does not consider the need for subsequent analysis of samples and processing of data acquired during the study, which continue well after a patient's final visit. For example, if a trial involves whole exome sequencing, the final clinical endpoint does not accurately capture the end of a significant portion of the experimental work.

The Endocrine Society appreciates that the results of clinical trials funded by the NIH should be made more transparent and accessible for researchers and the public. However, due to the concerns articulated above, we urge the NIH to incorporate our recommendations into the final policy. We believe that, after taking the recommendations into account, the new policy will facilitate the NIH mission to "advance the translation of research results into knowledge, products, and procedures that improve human health." Thank you for considering the Endocrine Society's comments. If we can be of any assistance in your efforts, please do not hesitate to contact Dr. Joseph Laakso, Associate Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

A handwritten signature in blue ink that reads "Richard J. Santen".

Richard J. Santen, MD
President, Endocrine Society

From: albertdonnay@gmail.com on behalf of [Albert Donnay, MHS](#)
To: [OCRBP-OSP](#)
Subject: Public Comment on NOT-OD-15-019
Date: Tuesday, February 10, 2015 5:38:38 PM

2/10/2015

Public Comment on NOT-OD-15-019:
Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

Thank you for the opportunity to provide comment.

As both a researcher and research volunteer concerned with how potential risks are disclosed to human subjects in clinical trials, I recommend that the NIH Office of Clinical Research and Bioethics Policy make four additions to the draft posted at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html> :

1) Please require all human clinical trials to submit as part of their initial registration a PDF of whatever IRB-approved Informed Consent [IC] form(s) they are asking their subjects [or their legal guardians] to sign, or their waiver if the IRB decided no IC was needed. Clinical trials should not be allowed to complete the registration process until they submit this. The obvious benefit of such a requirement is that it would reduce the number of human trials conducted without any informed consent.

2) Please post links to all the IC forms and waivers posted in ClinicalTrials.gov and create a searchable database of them so they can be selected by Boolean operators for any combination of specific risks, drugs, devices, clinical conditions, principal investigators, or institutions that they mention. [The ability to search for character strings both across and within millions of PDFs is available from Adobe, Alchemy and other enterprise-level document management software.]

Being able to search IC forms and waivers will permit IRBs, regulators, researchers, and subjects to compare the adverse events reported by studies of various drugs, devices and other interventions with those foreseen and disclosed in advance.

Assuming most IC forms and waivers are legitimate, IRBs and researchers should have no objection to posting them at clinicaltrials.gov, or at least posting those sections that discuss potential risks to human subjects.

3) Please require researchers to submit full citations for any papers or other forms of publication that result from their clinical trial, whether a full length paper or just an abstract or letter. They should provide and NIH should post a link to each cited publication, preferably to the publisher's website and either free online or behind a paywall as the case may be. Principal investigators should be given some time reasonable time limit for reporting this, such as 30 or 60 days from publication.

If any of the publications resulting from the trial are ever corrected or retracted, this should generate a new citation which the principal investigator should similarly be required to submit to clinicaltrials.gov for posting. .

4) To better protect public health and safety, please ask FDA to copy clinicaltrials.gov in real time on any and all warning letters or expressions of concern that it sends to the principal investigators of human trials. Clinicaltrials.gov should publish the full text of these letters unless FDA objects, and should at least publish their dates so anyone who is interested can followup with the principal investigators to whom they were addressed or request a copy from FDA via a FOIA request.

Thank you for your consideration.

Albert Donnay, MHS
PhD Candidate UMB
Program in Toxicology
albertdonnay@gmail.com
410-889-6666

From: [Bron Kisler](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Bron Kisler](#); [Rebecca Kush](#)
Subject: CDISC Response to NOT-OD-15-018
Date: Friday, February 13, 2015 11:04:06 AM
Attachments: [CDISC Response CTRegNPRM Final.docx](#)
[ATT00001.htm](#)

Please see attached CDISC's response to NOT-OD-15-018: Publication of Notice of Proposed Rulemaking for Clinical Trials Registration & Results Submission under FDAAA. Let us know if there are any follow-up questions. We will be glad to help.

Kind Regards — Bron

CDISC Response to NOT-OD-15-018

Publication of Notice of Proposed Rulemaking for Clinical Trials Registration and Results Submission under FDAAA

We strongly encourage NIH to harmonize the data formats for reporting clinical trial registration and results with current and emerging global standards rather than taking a proprietary approach. The opportunity now exists for NIH to join a collaborative and ongoing CDISC standards development project to ensure a single, global standard is available and adopted for a common purpose to improve transparency in research. Transparency cannot be reached without data standards.

According to WHO (and as presented in April 2014 at the CDISC Interchange in Europe), all clinical trial registries around the world -- with the exception of ClinicalTrials.gov -- are using the same 20 clinical trial registry elements, which are submitted to the WHO's International Clinical Trial Registry Platform (ICTRP) using a common XML format. A common Registry standard is being updated and expanded, at the request of a number of stakeholders through a collaborative CDISC project (CTReg) that includes representatives from WHO, EMA (European Medicines Agency), EFPIA (European Federation of Pharmaceutical Industries & Associations), and NIH/NCI building upon earlier work developed through HL7.

The PHS document referenced in the NPRM, states:

(vi) Consideration of World Health Organization data set

The Secretary shall consider the status of the consensus data elements set for reporting clinical trial results of the World Health Organization when issuing the regulations under this subparagraph.

The new data format, which is expected to be used by WHO and EMA for populating ICTRP and EudraCT database, will be a CDISC CTReg XML standard, aligned and consistent with other CDISC standards including those required in FDA binding guidance for electronic submissions of product marketing applications. The CTReg project will result in an XML schema based on the CDISC ODM standard, building upon the WHO Trial Registration Data Set (Version 1.2.1) of 20 elements (<http://www.who.int/ictrp/network/trds/en/>) currently being used by registration authorities throughout the world. This is taken from the CDISC Protocol Representation Model

<http://www.cdisc.org/protocol> and study descriptive metadata, submitted in CDISC SDTM format by sponsors to FDA as part of regulatory submissions.

The production release of the CDISC CTReg standard, which will be completed in 2015, should address the primary needs of ClinicalTrials.gov and can be extended to include additional requirements as they emerge. Use of a common standard will provide consistent metadata such that clinical trial information can be readily searchable around the globe. This standards development effort is also engaging Cochrane, CONSORT and COMET. Although there may not be complete agreement on all elements for all parties, it is important to ensure there is a consensus-based standard data format for the common elements across all parties. This will improve transparency and accessibility to information.

Regarding the submission of results, CDISC respectfully requests NIH consider adopting a standard data format consistent with CDISC standards (e.g. SDTM, ADaM). Data Submission Standards for subject level data, which have already been committed to by FDA and are in wide use among researchers around the world to support similar listings as described in ICH-E3.

Rather than develop another new approach for trial registration and results reporting, NIH should collaborate with CDISC, industry, WHO, FDA, EMA and others toward a common standard format for publishing Registration and Results data, which can: (1) be implemented consistently among global clinical research organizations; and (2) improve the transparency of research to all stakeholders. We ask NIH to consider encouraging researchers to use and adopt CDISC standards, joining the FDA, Japan's PMDA, EMA, WHO and industry toward making research data more accessible and usable for all.

From: [Adam Sulhunt](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Clinical Trials Transparency
Date: Tuesday, February 17, 2015 10:53:42 AM

Dear NIH

I fully support the [new proposals by the US Department of Health and Human Services \(HHS\) and National Institutes of Health \(NIH\)](#) to expand reporting of clinical trial results, and to make this a condition of research funding. These new regulations are vital as at present, the pharmaceutical industry are able to distort evidence and trial results, making it unclear what the best treatment for patients is, and thus exposing them to unnecessary harm. In addition, when data is unpublished, the patients who participate in these trials and put their bodies on the line for something they are told will contribute to the advancement of scientific knowledge, they are being lied to and betrayed.

I would also like to see researchers put their results on publicly accessible registers, in useful, standardised formats.

Kind regards

Adam Sulhunt



University of California
San Francisco

February 17, 2015

Office of the Executive Vice
Chancellor and Provost

513 Parnassus Avenue, S-115
San Francisco, CA 94143-04DD
Tel: 415/476-4451
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Daniel Lowenthal, MD
Executive Vice Chancellor
and Provost
Dr. Robert B. and Mrs. Blinzer Aird
Professor of Neurology

email: lowenthal@medschool.ucsf.edu

Re: Notice of Proposed Rulemaking (**NPRM**) for Clinical Trials Registration and Results Submission (**RIN 0925-AA52**, Docket Number **NIH-2011-0003**)
Jerry Moore, NIH Regulations Officer, Office of Management Assessment
[www.regulations.gov]

Re: Proposed NIH policy on Dissemination of NIH-Funded Clinical Trial Information (**NOT-OD-15-019**)
Office of Clinical Research and Bioethics Policy Office of Science Policy, National Institutes of Health (clinicaltrials.disseminationpolicy@mail.nih.gov)

To Whom This May Concern:

I am writing on behalf of the University of California, San Francisco (UCSF), to comment on the National Institutes of Health's Notice of Proposed Rulemaking (NPRM) for submitting registration and summary results information, including adverse event information, for specified clinical trials of drugs (including biological products) and devices and for pediatric postmarket surveillances of a device to ClinicalTrials.gov, the clinical trial registry and results data bank operated by the National Library of Medicine (NLM).

UCSF supports many of the proposed requirements for ClinicalTrials.gov registration and results reporting, however we identified a number of proposed rules that would benefit from additional clarification, and a few issues that merit further consideration. Our Protocol Registration System (PRS) administrators at UCSF currently oversee approximately 1,000 records, and our experience implementing the existing regulations informed our comments on the proposed rules. The UCSF response to NIH's NPRM comprises two parts: (I) comments on specific provisions of the NIH NPRM document; and (II) general comments.

I. Comments on specific provisions of the NIH NPRM document.

Due to the breadth of the NPRM, we limited the scope of our comments to the proposed rules that represent our greatest areas of concern. Excerpts of the relevant NPRM text are provided below for context, followed by our comments in *italics*.

Overview of Proposed Rule 111-C. Key Issues considered in this proposed rule
7. Submission of the protocol (FR 69582)

The proposal to require full protocols is unnecessary because the registration and results elements required under current rules provide sufficient information for both compliance and public information. Given that protocol documents contain proprietary information, redaction standards should be established before the rule is implemented.

Overview of Proposed Rule 111-C. Key Issues considered in this proposed rule
9. Retroactive submission of additional results information (FR 69583)

As described in section 111.D of this preamble on Effective Date, we do, however, propose to require the responsible party for an applicable clinical trial that reaches its completion date prior to the effective date of the final rule to submit all of the results information specified in proposed § 111.48 if the responsible party has not submitted results information prior to the effective date of the rule.

This proposed rule would create a significant burden for Academic Health Centers (AHCs) and investigators. UCSF, along with many other AHCs, is already expending considerable resources to support investigators' compliance with FDAAA results reporting requirements. AHCs are also working through a substantial backlog of results submissions, including for studies originally registered and owned by NIH, whom investigators have left the institution, retired or are deceased. The backlog includes older studies that were not designed or budgeted with awareness of FDAAA or the conservative OMB estimated 41 work hours to comply with results reporting. It is already difficult and time-consuming to retrospectively locate and summarize results data in the required format and requiring additional information will only increase noncompliance and divert resources from other areas of research compliance.

One way to alleviate the financial burden would be to allow registration and results reporting to be addressed in federal grants budgets as direct costs to the grant, whether incurred directly by the investigator or shared with a central administration unit. Federal funding agencies should also study actual burden (as opposed to projected estimate) for assuring compliance with all registration and reporting requirements.

Overview of Proposed Rule III • C. Key Issues considered in this proposed rule

12. Quality control procedures (FR 96584)

Consistent with the proposal in § 11.66 regarding correction of clinical trial information, responsible parties would be required to correct the errors, deficiencies and/or inconsistencies not later than 15 calendar days after being informed of them by the Agency or otherwise becoming aware of them (e.g., if they discover the errors, inconsistencies, and/or deficiencies themselves), whichever is later.

A mixture of 30-day and 15-day windows increases the complexity of understanding and complying with reporting and updating requirements. We suggest that a 30-day standard window for all deadlines is more understandable and practicable; shorter windows do not seem to provide increased benefit to information seekers relative to the costs of enforcement and compliance.

In addition to complexity posed by having windows of various duration, a 15-day window to correct errors may create a burden for investigators, and a 30-day window would be more appropriate; in many cases 15 days would be sufficient but in cases where the changes are complex this would not allow for sufficient time to produce additional statistical output if required plus proper internal review and approval processes.

Overview of Proposed Rule III c. Key issues considered in this proposed rule

13. Updating submitted clinical trial information (FR 69587)

Proposed § 11.64(b) identifies several data elements that must be updated not later than 30 days after a change occurs (e.g., Overall Recruitment Status and Availability of Expanded Access), requires updates to U.S. FDA Approval, Licensure, or Clearance Status not later than 15 calendar days after the change occurred, and specifies that if a protocol is amended in such a manner that changes are communicated to participants in the clinical trial, updates to relevant clinical trial information must be submitted no later than 30 calendar days after the protocol amendment is approved by the human subjects protection review board.

For updating clinical trial registration information, a mixture of 30-day and 15-day windows significantly increases complexity of understanding requirements and decreases likelihood of compliance. A 30-day standard for all deadlines would be more understandable and practicable; shorter windows do not seem to provide increased benefit to information seekers relative to the costs of enforcement and compliance.

Overview of Proposed Rule III - D. Effective Date/Compliance Date

4. Results information (FR 69593)

The Agency proposes to exercise its authority under section 4020(3)(D)(iv)(II) of the PHS Act in situations when partial results are due on or after the effective date of the rule to require the responsible party to submit clinical trial results information under proposed § 11.48 for all outcome measures, including primary outcome measures submitted prior to the effective date of the rule.

Updating previously approved outcome measures that have passed NJHIPRS quality review may present a significant burden for investigators. Considering that studies completed prior to the effective date were not designed or budgeted to comply with the new requirements, some investigators may be unable to comply.

Attempting to comply or explaining to PRS why compliance is not possible will be very time-consuming to investigators, PRS administrators at the institution, and PRS viewers.

Subpart a General Provisions § 11.4

(3) *Withdrawal of the designation of a principal investigator as the responsible party.* (i) In the event a principal investigator who has been designated the responsible party becomes unable to meet the requirements for being so designated under paragraph (c)(2)(i) of this section, the principal investigator must withdraw the designation in the form and manner specified at <http://prsinfo.ClinicalTrials.gov>, at which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section. (11) In the event a principal investigator who has been designated the responsible party is unable because of death or incapacity to withdraw his or her designation, the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section.

Under such circumstances, we suggest the sponsor could submit a waiver of results requirements. This would allow for the record to be closed from the Institutional account and posted on the public site with a notice of the reason that the study was terminated and only partial results (if any) were obtained. UCSF PRS administrators have had the experience of completing results for studies that were terminated due to death or refraction of investigators. Although the studies were abandoned and no analyses were performed, there was no mechanism to remove the problem records from the institutional account. These situations cause an enormous burden on institutional resources. Much time is spent attempting to locate abandoned data and composing language that satisfies PRS reviewers; but the posted information often does not provide benefit to the public or the scientific community. Considerable PRS reviewers' time is also spent advising investigators and AHC, PRS administrators through the process.

Subpart a General Provisions § 11.10

Completion date means, for a clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes.

We strongly support retaining use of the term "Primary Completion Date" since the concept that a study is "Completed" but can still be "Active, not recruiting" seems mutually exclusive, and a clear definition of Primary Completion Date could fulfill the same purpose. A PRS-specific definition of "Completion Date" may cause confusion and lead to posting of inadvertently incorrect information. "Primary Completion Date" is recognizable to current users of the system and is a term whose definition is less likely to be "assumed" and misinterpreted by both experienced and inexperienced PRS users.

Subpart a General Provisions § 11.10

Outcome measure means a pre-specified measurement that will be used to determine the effect of experimental variables on the human subjects in a clinical trial. See also primary outcome measure and secondary outcome measure.

We strongly suggest that the NIH provide additional resources and training to help investigators understand the particular structure and specificity required for the statement of Outcome Measures. This section triggers the most QA Comments and presents a significant burden to PRS Administrators attempting to assist investigators with registration, responding to QA comments, and results reporting.

Subpart a General Provisions § 11.10

(14) *U.S. FDA Approval, Licensure, or Clearance Status* means, for each drug or device studied in the clinical trial, whether that drug or device is approved, licensed, or cleared by the U.S. Food and Drug Administration for any use.

Approval status for the indication may be an informative option, e.g., "Approved but not for use being studied"

Subpart a General Provisions § 11.10

(16) *Study Start Date* means the estimated date on which the clinical trial will be open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled.

We consider studies to have "started" when they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled. Clinica/Trials.gov could call this field "Date of First Enrolled Participant," instead of Study Start (anticipated and actual).

Subpart a General Provisions § 11.10

(20) *Secondary Outcome Measure Information* means a description of each secondary outcome measure, to include the following information: (i) Name of the specific secondary outcome measure; (ii) Description of the metric used to characterize the specific secondary outcome measure; and (iii) Time point(s) at which the measurement is assessed for the specific metric used.

Please clarify whether outcome measures that are not part of the analysis plan, OR indicated to be exploratory or tertiary, are not required; Zarin et al. (NEJM 2015) does not contain the "of" statement.

Our understanding is that the presence of an analysis plan does not change the nature of an exploratory outcome measure to any other outcome measure type.

Subpart a General Provisions § 11.10.

(29) *Availability of Expanded Access* means, for an applicable drug clinical trial of a drug that is not an approved drug: (i) An indication of whether there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) for those who do not qualify for enrollment in the applicable clinical

Please clarify: Does this apply only to Expanded Access (EA) clinical trials under the same sponsor-investigator as non-EA trials using the same drug? If not we would suggest that FDA require manufacturers to notify all investigators who are studying a drug when any EA becomes available. Would NIH recommend that investigators seek agreement from manufacturers to provide notification of any EA records throughout the duration of the investigator-initiated trial of the same drug? Could PRS notify investigators when expanded access record is created for the same drug that they're studying?

Subpart C Results Submission § 11.48

(v) *Statistical Analyses*. Result(s) of scientifically appropriate statistical analyses, if any, including any statistical analysis that is: (A) Pre-specified in the protocol and/or statistical analysis plan that was performed on the outcome measure data, (B) Made public by the sponsor or responsible party prior to the date on which results information is submitted for all primary and secondary outcome measures studied in the clinical trial, or (C) Conducted in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial. Submitted Statistical Analysis information must include:

Please clarify: Will all statistical analyses - not just primary analysis - published in a manuscript be reported under criterion B, even if exploratory, post-hoc, and/or sub-group analyses? There might be hundreds of additional analyses in some cases, which could represent a very significant burden to the responsible party, particularly when reporting in PRS was not previously planned or budgeted. Furthermore, without explanatory context (which is not permitted) posting of exploratory or post-hoc analyses could be misleading or confusing to readers. Moreover, PRS would need major expansion to include all the possible statistical analyses this could encompass that are not current options to select in the system.

Please Note We suggest that Clinica/Trials.gov results reporting requirements be accepted in similar formats to reduce duplicative efforts when results are required to be reported to NIH or other Federal funders (e.g., CTRP for NCI). Results submitted to NIH or other Federal Funders should contain sufficient information and be in a format with which upload, or link acceptable to Clinica/Trials.gov.

Subpart C Results Submission § 11.48

(1) *Statistical Analysis Overview*: Identification of the arms or comparison groups compared in the statistical analysis, the type of statistical test conducted; and, for a non-inferiority test, a description of the analysis that includes, at minimum, the power calculation and non-inferiority margin;

NPRM: We invite comment on whether the list of proposed options is sufficient for all applicable clinical trials or voluntarily submitted clinical trials for which statistical analysis information might be submitted to ClinicalTrials.gov under this **proposed** rule.

Thank you for the opportunity to comment. The structure and dropdown choices throughout the statistical analysis section appear to be too rigid and limiting to accommodate non-drug/device studies and smaller (investigator-initiated) studies. Exempting non-industry or non-drug/device studies from this requirement may be an appropriate alternative to the myriad of choices and free-text descriptions needed to accommodate all types of analyses in all types of trials. In the absence of such an exemption, at minimum, a much more robust backdrop of explanations/definitions/guidance in PRS will be needed to enable individual investigators to report statistical analyses correctly, including categorizing the "Type of analysis," without undue burden.

The limited selections for "type of analysis" may be difficult and burdensome for behavioral trials and Phase I-II trials. Individual investigators, particularly those in social or behavioral sciences and new to ClinicalTrials.gov, may not understand how to categorize various types of analyses. Unless only superiority, non-inferiority, or equivalence analyses will be required to report results, an option is needed for "Other" type of analysis. "Not applicable" is a term commonly understood to mean that a question is not relevant to the situation. However, any analysis is a "type of analysis"; therefore, "other" is more appropriate than "Not applicable" for analyses other than efficacy comparisons. Examples: variability estimate for sample size calculation of a larger RCT; trials with qualitative outcomes for feasibility and/or acceptability; trials including analyses for specificity, sensitivity, correlation, validity, reliability, inter-examiner reliability, etc. Please explain whether only those analyses comparing intervention to control will be required in results reporting; if not, please provide a less structured format and much more detailed guidance in consideration of non-industry, non-drug/device studies with outcomes that may not be efficacy comparisons.

Subpart C Results Submission § 11.48

(6) Information for each table specified in paragraph (a)(4)(i) of this section must include the following elements: (D) Total Number Affected, by Organ System

The requirement to summarize adverse events by organ-system presents a significant burden for Investigator-Initiated studies at AHCs:

- Investigator-sponsors usually do not have access to or use MedDRA (Organ system) to record AEs
- PRS Administrators and investigators at UCSF, as well as our colleagues at other AHCs, report that they manually add organ-system to each AE entry in ClinicalTrials.gov, only because it is required in ClinicalTrials.gov. Those without access to MedDRA are choosing the organ-system for each AE using best judgment. Unless all clinical trials are required to use MedDRA as a standard vocabulary for reporting, providing the MedDRA organ-system in ClinicalTrials.gov has been and will continue to be a burden to studies not otherwise using MedDRA coding.
- The additional requirement of total number affected by organ-system will add a significant burden for investigator-initiated studies at AHCs. For example, if the organ-system field is not recorded as part of the original study conduct, it is currently added to each AE entry at the time of results reporting. The proposed requirement to summarize by organ system will require that the extra field be added to each AE in a dataset outside of ClinicalTrials.gov to be able to run a summary report (SAS, SQL) prior to data entry for results reporting. Output from such a report would then be manually entered into ClinicalTrials.gov. The data-enhancement (with organ-system) and summary report programming is a level of analytic support not currently available to investigator-initiated studies. Studies active as of the effective date, and those that are completed with results in preparation, have not budgeted for the resources needed to comply with additional programming and reporting requirements

- Industry studies do subscribe to MedDRA, and have the infrastructure, expertise, and experience to run grouping summaries; thus, this new requirement may not raise concerns from Industry. This is not so for individual investigators at AHCs.

Proposed alternative(s):

- Do not require organ-system for AEs if data not used in marketing application
- Do not require organ-system for non-industry/AHC AE reporting (sponsor-investigator)
- Do not require organ-system for non-FDA-regulated interventions
- If Investigator-initiated studies at AHC's will be required to summarize AEs by organ-system, provide PRS tools to automate the summary. In other words, an option to load full-detail event-level AE data into PRS for automatic generation of the summary to **be made** public:
 - *Le., provide field-by-field dataset specifications for event-level AE data to upload, upon which PRS will generate the required reporting summaries: For example, date of event, subject ID, study arm, event, organ-system*

General comment: Much of the language and guidance for results reporting in ClinTrials.gov seems to assume that all studies have a sophisticated infrastructure, as do industry studies of FDA-regulated products. It has been difficult for individual investigators at AHCs to understand and comply with the requirements for their "Applicable Clinical Trials." Expansion of results-reporting requirements to non-drug/device studies conducted by investigators unfamiliar with ClinTrials.gov will create a much greater need for detailed and accessible guidance, tools, and structure to make the system understandable and navigable to individual investigators outside of Industry.

NPRM: We invite public comment on the **proposed approach**, experience to date with the current approach, and other information that might be collected on a voluntary basis.

Thank you for the opportunity to comment on experience to date with the current approach: Small investigator-initiated studies in academic institutions typically do not have the computing/programming/analytic support needed to generate summaries of AE data in the detail required. Experience to date includes time-intensive post-hoc sorting and manipulation of AE data in Excel to mostly-manually count frequencies. Requiring frequency by organ-system-classification will exceed our abilities to comply for investigator-initiated studies, most of which will not have adequate budget for additional programming support to apply complex summarizing and grouping logic to AE data for results reporting.

While our institution is exploring options and seeking resources to inform and support our investigators in this area, and there are many online examples of programming code that may be used for AE summaries, we request that the PRS embed a program to generate AE summary tables using an uploaded dataset formatted according to PRS specification. This would not only help small studies that do not have the budget for programming support, but also would help ensure that summaries are uniform and correct in their grouping logic.

Subpart C Results Submission § 11.48

(f) Information for each table specified in paragraph (a)(4)(i) of this section must include the following elements:

(E) Total Number at Risk, by Organ System.

Since the number at risk for the arm is likely to be the number at risk for each organ system, we suggest that the number at risk "by organ system" default to the number at risk for the entire treatment arm. Please provide examples of how a participant may not be at risk for a specific organ-system-class AE.

Subpart C Results Submission § 11.52

5. When will NIH post submitted results information? Proposed § 11.52 provides that the Director will post results information not later than 30 days after the date on which the information is submitted to the agency for an applicable clinical trial.

We are concerned that results may be posted that have not passed QA review. Suggest that language should indicate that results must pass QA review prior to public posting.

Of additional concern to investigators is whether journals/ editors will continue to interpret ClinicalTrials.gov results reporting as non-publication of results given the increased results requirements. Please see below from the ICMJE website- <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>

"Will the ICMJE consider clinical trial results posted at ClinicalTrials.gov in compliance with the Food and Drug Administration Amendments Act of 2007 to be prior publication? It is important to note that the ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. While the ICMJE recognizes the potential problems associated with posting preliminary research results that have not yet undergone an independent peer review process, it acknowledges that the Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII), mandates the posting of summary results data for certain trials in ClinicalTrials.gov. Thus, the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication. The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting."

How will investigators know if ICMJE is going to expand their requirements or if the additional requirements for results will qualify as prior-publication? A possible solution would be to comply with ClinicalTrials.gov requirements and submit results within 12 months of the last follow-up of the main outcome measure of the last participant, but withhold full public release of the results for up to another 12 months while papers are in pre-publication peer review and revision.

Subpart D Additional Submissions of Clinical Trial Information § 11.64

(Q) If the first human subject was not enrolled in the clinical trial at the time of registration, the Study Start Date data element must be updated not later than 30 calendar days after the first human subject is enrolled.

Many investigators and IRBs often consider studies to have "started" when they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled. Suggest ClinicalTrials.gov name this field "Date of First Enrolled Participant" (anticipated and actual), instead of Study start Date.

Subpart D Additional Submissions of Clinical Trial Information § 11.64

(2) Updates to the U.S. FDA Approval, Licensure, or Clearance Status data element must be submitted not later than 15 calendar days after a change in status has occurred.

A mixture of 30-day and 15-day windows increases the complexity of understanding and complying with requirements. We strongly support that a 30-day standard window for all deadlines is more understandable and practicable; shorter windows do not seem to provide increased benefit to information seekers relative to the costs of enforcement and compliance.

Subpart D Additional Submissions of Clinical Trial Information § 11.64

(2) The Director will retain prior clinical trial registration information and clinical trial results information and make it publicly available in accordance with § 11.35 and § 11.52, respectively, through ClinicalTrials.gov so that the updates do not result in the removal of any information from the original submission or any preceding update.

NPRM: We invite public comments on our proposed approach and alternatives.

Thank you for the opportunity to comment. We think this presents the potential to confuse or mislead public who may inadvertently access incorrect information. If errors are discovered during manuscript preparation or peer-review of a manuscript the investigator would correct any results already posted in ClinicalTrials.gov. What is the purpose of retaining and making public the incorrect information? An alternative solution would be to retain the incorrect submission, but not make it publicly available, or available only by written request, and ensure that the requestor understands that they may be receiving incorrect information.

Subpart D Additional Submissions of Clinical Trial Information § 11.66

(a) *Correction of errors.* A responsible party who becomes aware of errors in any clinical trial information submitted under this part or is informed by NIH that such clinical trial information contains errors shall correct such errors not later than 15 calendar days after the date on which the responsible party becomes aware of the errors or on which NIH informs the responsible party of the errors, whichever is earlier.

15 days may be too short a time to post corrected results in some cases, e.g. reopen database, conduct reanalysis, internal review. Recommend additional framework to address this possibility. For example, pulling the record from public view while the sponsor tries to sort out the issue and determine if changes need to be made to the record. The difficulty and burden of compliance may be considerable, and provide little or no benefit.

II. Our General Comments about the Proposed NIH Policy and the NPRM

The proposed NIH Policy complements the NPRM in that it would apply to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the rules proposed in the NPRM."

While we support the spirit of open access to data from any phase clinical trial, we believe the NIH's own policy on data and safety monitoring plans for clinical research studies where the level of monitoring is commensurate with the scope of the study and safety concerns should be taken into consideration regarding ClinicalTrials.gov results reporting. Navigating the PRS to report results for small and early phase trials that do not have the budget or staff to prepare such reports will be burdensome.

Infrastructure Needed

While we support the proposed requirements for ClinicalTrials.gov registration and results reporting, it is important to keep in mind that ClinicalTrials.gov registration and specifically, results reporting are complex processes. The proposed NPRM can provide clear guidance, but successful implementation will also require IT solution for data/workflow management from NIH and the PRS system. Currently, the effectiveness and efficiency of ClinicalTrials.gov administrators at AHCs is severely hampered by the limitations of the PRS system, most notably the inability to sort, filter, or generate reports using any or all fields in the records of the institutional account. In our experience, this is one of the most complex pieces of necessary IT infrastructure that requires as careful consideration and improvement as does the implementation plan to accompany this NPRM.

Suggestions

At UCSF we are currently the administrators for 1000 ClinicalTrials.gov records. Many AHCs have similar volume. When compared to the lower volume of records managed by industry, the NPRM would pose a disproportionate burden on AHCs. For example, industry AE reporting fits the proposed NPRM format whereas for AHCs it would be a significant change in reporting AEs.

The very significant burden of the proposed changes on both investigators and PRS administrators could be partially alleviated by improved communication, notification, information resources (reports, filters), and navigation in the PRS. NIH should consider an effort to improve its communications relative to PRS users, including the regularity of email reminders and problem notices. Moreover, either grandfathering trials that have already started or pushing back the implementation date or providing supplemental funds to cover the burden (OMB very conservatively estimates 41 work hours, and we believe it will be much greater) would enable better communication about and compliance with these changes.

NPRM Timeline for Comments

Regarding the February 19, 2015 deadline for comments, UCSF PRS administrators and users (i.e., investigators) need more time to address specific issues. As previously suggested, ClinicalTrials.gov should consider different requirements for AHCs vs. industry as many of the requirements seem to apply more to industry than AHCs. As mentioned above, industry AE reporting fits the required format whereas for AHCs it would be a significant change in reporting AEs.

Would ClinicalTrials.gov consider additional time, tools, or waivers for these requirements? These burdens seem to apply disproportionately to individual investigators and PRS administrators at AHCs rather than industry.

III. Conclusion

In closing, UCSF agrees with the plan for an expanded registry and results data bank specified in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials.

However, in our experience, the details currently missing in the NPRM and outlined in our comments are not trivial and will require careful consideration in order to achieve the effects that NIH is looking for. To that extent, UCSF remains available to help shape the further details of this important NPRM Initiative.

Thank you for this opportunity to comment.

Sincerely,

(Daniel H. Lowenstein)

Daniel H. Lowenstein, MD
Executive Vice Chancellor and Provost
Dr. Robert B. and Mrs. Ellinor Aird Professor of Neurology

From: [Laura Levit](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: ASCO's comments on the draft NIH policy
Date: Wednesday, February 18, 2015 9:49:43 AM
Attachments: [ASCO's Comments to NIH.pdf](#)

Hello,

The attached file contains the American Society of Clinical Oncology's (ASCO's) comments on the NIH proposed rule and draft policy on clinical trials registration and results submission.

Please let me know if you need any additional information.

Best,
Laura

Laura Levit, JD

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Making a world of difference in cancer care

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February 18, 2015

Francis S. Collins, MD, PhD

Director

National Institutes of Health

9000 Rockville Pike

Bethesda, Maryland 20892

Subject: Proposed Rule and Draft Policy on Clinical Trials Registration and Results Submission

Dear Dr. Collins:

Thank you for the opportunity to provide input on behalf of the American Society of Clinical Oncology (ASCO) regarding the proposed rule and draft policy on clinical trials registration and results submission. ASCO is the leading professional organization representing oncologists and other health care professionals who care for people with cancer and conduct research to improve cancer treatment. With more than 35,000 members, ASCO is committed to improving cancer care through scientific meetings, educational programs, defining and measuring the quality of cancer care, and publishing peer-reviewed journals.

ASCO strongly supports the National Institutes of Health's (NIH's) efforts to clarify and improve its rules regarding the registration and sharing of clinical trial data. The increased availability of clinical trial information has the potential to increase trial participation and expand the impact and value of the contributions made by trial participants. Specifically, we strongly support the following provisions of the proposed rule and draft policy:

- **The new data elements required for registration and results submission.** ASCO supports the goal of using information provided during registration (rather than requiring a separate data element) to determine whether a trial is an applicable clinical trial under the rule because this reduces administrative burden.

- **The requirement that some information be provided in a structured format.** The data in ClinicalTrials.gov are only valuable to the extent that they are high-quality and well organized, and are standardized across entries. ASCO is particularly supportive of requiring more structured data elements because this will make it easier for users of the data to search for information and integrate it with other datasets. ASCO is in the process of developing CancerLinQ, a learning health care system that will allow clinicians to analyze aggregated, real-world cancer clinical data from electronic health records (EHR). Including structured data elements in ClinicalTrials.gov will enable systems such as CancerLinQ to build algorithms to facilitate matching of patients to clinical trials with appropriate eligibility criteria.
- **The requirement that all applicable trials (not just those for which the drugs or devices studied are FDA approved, licensed, or cleared) report results information.** This increased transparency will provide researchers with important information about existing treatments as well as those in development. It may create opportunities to verify findings, develop an expanded understanding of how to use products (including for new indications), identify rare but serious side-effects, advance research to develop new treatments, and improve our understanding of the heterogeneity of the disease process. In addition, the data could help improve the efficiency and reduce the costs of the clinical trial process by minimizing redundant trials.
- **The requirement for sponsors to include an expanded access record if a drug studied in an applicable clinical trial is also available through an expanded access program.** Providing clarity and transparency to the process for accessing investigational agents is an important step to ensuring that patients are aware of all possible treatment options and, that when appropriate, clinicians can easily navigate the expanded access process for their patients.
- **More frequent updating schedule.** It is a longstanding and firmly held belief in oncology that the option to participate in a clinical trial is a key component of high-quality cancer care and should be a readily accessible option for any cancer patient. ClinicalTrials.gov is only valuable to clinicians and patients in identifying potential trials to the extent the information is complete and up-to-date. The stricter deadlines proposed by NIH on when data elements would need to be updated furthers this goal.
- **The recognition that applicable clinical trials include single-arm trials.** Increasingly, many trials in oncology are single-arm and compare the effect of an intervention to an historical control or baseline data. It is important for transparency and comprehensiveness that these trials be included in ClinicalTrials.gov.

As NIH finalizes its rule and policy, we hope it will consider clarifying the following issues:

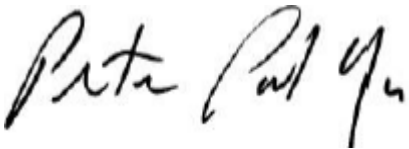
- **NIH should consider requiring information about the attribution of adverse events.** Cancer is a complex and deadly disease and trials often combine the investigational agent with standard of care treatments. Both of these facts make it difficult, at times, to

determine whether an adverse event is caused by the investigational agent, the standard of care agent(s), or the underlying cancer. Thus, it is important that the information on adverse events in ClinicalTrials.gov accurately reflect what information the researchers are reporting (i.e., whether the record includes all adverse events or only adverse events that the researchers believe are attributable to the study drug or intervention). Allowing researchers to link to existing publications or abstracts on the trial would also provide contextual information about the adverse events.

- **ASCO believes that adding a requirement for sponsors to list an investigational new drug (IND) number or make clear that a trial is IND-exempt would help with implementation of the Affordable Care Act provision requiring coverage of routine care costs of clinical trials (codified as 42 U.S.C. §300gg-8).** Currently, some insurers make burdensome requests for information to make a coverage determination about clinical trials (including a copy of the complete trial protocol). This new data element would help transform ClinicalTrials.gov into a one-stop resource for determining whether a trial qualifies for insurance coverage under the Affordable Care Act.
- **ASCO thinks that sponsors of all applicable clinical trials should submit the full protocol to ClinicalTrials.gov.** Requiring the full protocol would improve transparency by providing the public with maximal information about inclusion/exclusion criteria, the intervention being studied, and the trial endpoints. Submission of the protocol should be required for publicly funded trials. If commercial sponsors determine that the protocol includes trade secrets, this requirement could be met for these trials by redacting any proprietary information.
- **ASCO supports the requirement that clinical trials funded by NIH meet registration and reporting requirements.** ASCO is also supportive of expanding this requirement to phase I trials. Phase I trials have therapeutic intent and, increasingly, are being conducted with expanded cohorts to assess treatment efficacy. There are examples in cancer of the Food and Drug Administration approving new drugs on the basis of phase I results. The scope of this new policy, however, should be clarified to clearly exclude cancer care delivery research and quality improvement efforts. These activities are likely to lead to important improvements in patients' care, while putting participants at minimal risk. We do not want to discourage these activities by burdening them with undue reporting requirements.
- **Researchers' requests for funding to support ClinicalTrials.gov reporting requirements should be an allowable budget item in NIH grants.** This would ease the implementation of the draft NIH policy by providing researchers with the resources to meet these requirements. It would also align the new policy with the 2015 Institute of Medicine report, *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risks*, which recommended that sponsors and funders "provide funding to investigators for sharing of clinical trial data as a line item in grants and contracts." p. 5

We appreciate this opportunity to provide information on this topic and would be pleased to provide any additional information. As a professional society, ASCO believes it has a unique role to play in improving clinical trial registration and results reporting. We would welcome working more closely with NIH to promote research transparency. Please contact Laura Levit at laura.levit@asco.org or 571-483-1638 for any follow-up on this important topic.

Sincerely,

A handwritten signature in black ink that reads "Peter P. Yu". The signature is written in a cursive style with a large initial "P" and a long, sweeping underline.

Peter P. Yu, MD, FACP, FASCO
ASCO President

From: [Mary Langman](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comments on Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
Date: Wednesday, February 18, 2015 1:07:30 PM
Attachments: [2015_clin-trials_nih_joint-comments_final.pdf](#)

The attached comments are submitted on behalf of the Medical Library Association, Cancer Libraries Section of MLA and the Association of Academic Health Sciences Libraries.

--

Mary M. Langman
Director, Information Issues and Policy
Medical Library Association
65 E. Wacker Place, Ste. 1900
Chicago, IL 60601-7246
312/419-9094, ext. 27
312/419-8950 (fax)

Attend MLA'15 "Librarians Without Limits"
May 15-20, 2015 in Austin, TX

Comments of the Association of Academic Health Sciences Libraries (AAHSL), Medical Library Association (MLA), and Cancer Libraries Section of MLA

In Response to the NIH Notice of Proposed Rulemaking for Clinical Trials Registration and Results Submission under FDAAA

As health sciences librarians who fulfill requests for information from clinicians, scientists, and patients, we applaud NIH for proposing to expand the ClinicalTrials.gov requirements to all NIH clinical trials. As studies have shown, many “outcomes” of research studies are never reported in the literature for various reasons. This results in important data and scientific information being inaccessible that might inform future research discoveries, the design of new protocols, or decisions made by patients and health care providers. The research community and public should know when a study is closed due to adverse events, difficulties in research design making accrual difficult, or simply feasibility problems. Negative results also go unpublished which can lead others to try and repeat similar protocols. Knowledge of failed studies may also lead to scientists to try different approaches to the same or similar intervention. Ultimately, expanding the requirements will create an incredible and vastly important database of clinical data and knowledge for clinicians, scientists, and patients who need access to cutting-edge information.

From: [Renée Llanusa-Cestero](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information,
Date: Wednesday, February 18, 2015 2:32:33 PM
Attachments: [Llanusa_NIH-DisseminationPolicy.docx](#)

Attached please find my comments re the above-referenced.

Renée Llanusa-Cestero

Renée Llanusa-Cestero
[786-553-2303](tel:786-553-2303) cell

From: Renée Llanusa-Cestero, La Cesta Consultants, LLC, rlanusa@gmail.com

To: National Institutes of Health

Re: Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information, NOT-OD-15-019

Via: Electronic communication, clinicaltrials.disseminationpolicy@mail.nih.gov

Date: February 11, 2015

This comment is written in strong support of the draft NIH Policy to promote broad dissemination of clinical trial information from all NIH-funded awardees and investigators conducting clinical trials. The draft NIH Policy enhances transparency and “the change in cultural expectations” regarding trial disclosure.¹ This comment highlights the role of public policy in creating a research culture where maximizing social benefits is mandated as forethought through registration and submission of summary results via ClinicalTrials.gov. Moreover and importantly, the broad dissemination of summary trial results contributes to the ethical development of research by underwriting trust among volunteers, the public at large and clinical researchers. This comment:

- Locates the draft NIH Policy in the context of the ongoing development of a research culture that maximizes social benefits while minimizing risks to volunteers, and
- Proposes that, when the final NIH Policy is issued, specific procedural guidance be included for “a summary of the clinical trial and its results that is written in non-technical, understandable language.”²

Change in cultural expectations

The change in cultural expectations regarding trials disclosure is evidenced by calls for stakeholders to create a research culture that maximizes the social benefits while minimizing the risks to volunteers. Mandated summaries written in non-technical language understandable to research volunteers dates to the establishment of an online registry of clinical trials available at no charge to the public eventually known as ClinicalTrials.gov.³ The draft NIH Policy conforms to Executive Order 13563: promoting the selection of “regulatory approaches that maximize net benefits.”⁴ The Patient-Centered Outcomes Research Institute (PCORI), research arm of the Affordable Care Act, supports dissemination and implementation of study results reported “in a manner understandable to each target audience.”⁵ Coinciding with the publication of the draft

¹ Zarin, DA, Tse, T, Williams, RJ, et al. The ClinicalTrials.gov Results Database – Update and Key Issues. NEJM 2011;364:852-860.

² Section 801. Public Law No. 110-85. Food and Drug Administration Amendments Act of 2007. <http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>

³ Public Law No. 105-115, 113. Food and Drug Administration Modernization Act of 1997. <http://gpo.gov/fdsys/pkg/PLAW-05publ115/html/PLAW-105.html>

⁴ Executive Order 13563. Improving Regulation and Regulatory Review. (January 18, 2011). Federal Register 2011;76:3821-3823. <http://www.gpo.gov/fdsys/pkg/FR-2011-01-21/pdf/2011-1385.pdf>

⁵ Patient-Centered Outcomes Research Institute. 2013. Methodology Report. Appendix A Methodology Standards. <http://www.pcori.org/assets/2013/11/PCORI-Methodology-Report-Appendix-A.pdf>

NIH Policy is the Institute of Medicine (IOM) Report Brief *Sharing Clinical Trial Data Maximizing Benefits, Minimizing Risk*. The IOM Report Brief concludes that limited data sharing prevents maximum utilization of knowledge and provides a practical and ethical framework “to create a culture in which responsible data sharing is incentivized and best practices are disseminated widely.”⁶ The Executive Order, the PCORI Methodology Standards, the IOM Report Brief and the draft NIH Policy represent a renewed commitment to the *Belmont* ethical dictum “maximize the possible benefits and minimize the possible harms.”⁷

Implementing broad dissemination

Procedural guidance for the implementation of summary trial results written in non-technical language understandable to research volunteers and the public at large supports the purpose of the draft NIH Policy. Furthermore, compliance with the NIH Policy as a term and condition in the Notice of Grant Award and as a contract requirement in the Contract Award incentivizes the adoption of maximizing the social benefits of research as an essential element of the change in cultural expectations regarding the ethical conduct of clinical trials.

The inclusion of plain language summary results at ClinicalTrials.gov is a direct and simple expression of social justice. It demonstrates respects for research volunteers, the communities from which they are recruited and the public at large. It speaks directly to the people who materially support public-funded research.⁸ Plain language summary results published side-by-side with summary results addressed to the scientific community illustrates a form of ethical parity. The transparency, accountability and knowledge sharing demonstrated by the availability of summary trial results for scientists as well as volunteers and the communities from which they are recruited serves as a model of ethical conscientiousness for all human subject research.

⁶ Institute of Medicine. *Sharing Clinical Trial Data Maximizing Benefits, Minimizing Risk*. Report Brief. January 2015. <http://www.iom.edu/Reports/2015/Sharing-Clinical-Trial-Data.aspx>

⁷ National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. *The Belmont Report: Ethical principles and Guidelines for the Protection of Human Subjects of Research*. 1979. <http://www.hhs.gov/humansubjects/guidance/belmont/html>

⁸ Editorial. We Paid for the Research, So Let's See It. *New York Times*, February 25, 2013.

From: [Smith, Megan](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Ellerbe, Robyn Watson](#)
Subject: APTA Comments: Draft NIH Policy on Dissemination of NIH-Funded Clinical Trials Information
Date: Thursday, February 19, 2015 4:32:14 PM
Attachments: [APTA_20150213_NIH20110003.pdf](#)

Dear Mr. Moore,

The American Physical Therapy Association (APTA) is pleased to submit the attached comments in response to the "Announcement of a Draft NIH Policy on Dissemination of NIH-Funded Clinical Trials Information." We would like to thank the National Institutes of Health for the opportunity to comment on the draft policy and look forward to learning the final decision.

Sincerely,

Megan H. Smith, MLS
Research Specialist
American Physical Therapy Association
1111 N. Fairfax Street
Alexandria, Va. 22314-1488
703.706.3168 (phone)
800.999.2782, x3168 (toll-free)
megansmith@apta.org

American Physical Therapy Association - 1111 N. Fairfax Street, Alexandria, VA, 22314. 800-999-APTA (2782). To manage the types of e-mail messages you receive from APTA, please visit www.apta.org/email

1111 North Fairfax Street
Alexandria, VA 22314-1488
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J. Michael Bowers

Combined Sections Meeting

February 4-7, 2015
Indianapolis, IN

February 10, 2015

Jerry Moore
NIH Regulations Officer
Office of Management Assessment
6011 Executive Blvd, Ste. #601
MSC 6779
Rockville, MD 20852-7669

RE: AllTrials Campaign: Clinical Trials Registration and Results Submission
(Docket ID: NIH-2011-0003; RIN ID: 0925-AA52)

Dear Mr. Moore:

On behalf of the American Physical Therapy Association (APTA), we would like to thank the National Institutes of Health (NIH) for the opportunity to comment on the AllTrials Campaign.

APTA is a professional organization representing the interests of more than 90,000 physical therapists, physical therapist assistants, and students of physical therapy. APTA's goal is to foster advancements in physical therapist practice, research, and education and to further the profession's role in the prevention, diagnosis, and treatment of movement dysfunctions and the enhancement of the physical health and function of members of the public. Physical therapists perform evidenced-based examinations, screenings, evaluations, and interventions for musculoskeletal, neurological, cardiovascular pulmonary, and integumentary conditions and provide patient centered care that focuses on function and mobility to improve an individual's quality of life.

Role of the Physical Therapist in Rehabilitation Research:

Physical therapists conduct rehabilitation research that makes a difference in the lives of individuals with impairments, functional limitations and disability. Many physical therapist researchers study chronic conditions that have an impact on individual quality of life and on our health care system as a whole, in terms of cost and resource utilization. Advancements in rehabilitation research have led to improved quality of life for individuals who have spinal cord injuries, loss of limb, stroke and other orthopedic, neurological, and cardiopulmonary disorders.

Clinical Trials in Physical Therapy Journal:

Physical Therapy (PTJ) is the official scientific journal of the American Physical Therapy Association and the Royal Dutch Society for Physical Therapy (KNGF). PTJ engages and inspires an international readership on topics related to physical therapy. As the leading international journal for research in physical therapy and related fields, PTJ publishes innovative and highly relevant content for both clinicians and scientists and uses a variety of interactive approaches to communicate that content, with the expressed purpose of improving patient care. Authors submitting to PTJ are required to have their clinical trials registered. We publish both positive and negative trials in PTJ and make decision about publications based on the quality of the trials, not the results.

APTA Comments on the AllTrials Campaign:

APTA is in support of proposed regulations to implement report requirements for clinical trials that are subject to Title VIII of the Food and Drug Administration Amendments Act of 20017. It is our strong belief that all clinical researchers should be transparent in all NIH-funded clinical trials and that such clinical trials should be registered and the results reported, to include trials of unapproved, unlicensed, and un-cleared products.

We look forward to learning the final decision on this proposed rule. If you have additional questions, please feel free to contact Nancy White, PT, DPT, OCS, Chief Professional Affairs Officer, at 703-706-8594 or nancywhite@apta.org.

Sincerely,



Paul A. Rockar, Jr, PT, DPT, MS
President

PAR:rm

From: [Ross, Joseph](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Public Comments
Date: Thursday, February 26, 2015 9:58:43 PM
Attachments: [Public Comment for NIH Proposed Changes 15-02-24.docx](#)

The Yale University Open Data Access (YODA) Project at Yale University and the Yale-New Haven Hospital's Center for Outcomes Research and Evaluation (CORE) supports and applauds the draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information, expanding public availability of clinical trial summary results. While this is an important step forward in promoting the responsible and comprehensive dissemination of clinical research results, we believe that further steps can, and should, be taken to promote open science and share clinical research data.

The YODA Project strongly supports the proposal to extend reporting of summary results to all clinical trials conducted by all investigators receiving funding from the NIH. However, the YODA Project suggests that this policy would be stronger if the scope of these changes were expanded to include the availability of detailed summary results, such as Clinical Study Reports, as well as de-identified individual patient-level data.

The YODA Project also suggests a more detailed definition be developed to objectively define the term "health related biomedical or behavioral outcomes," which is used in the proposal to determine whether a study is deemed an "applicable" clinical trial by the NIH. The current definition allows for subjective judgments, which could lead to the exclusion of studies that contain valuable information for public health research, science, and clinical medicine. It is vital to recognize and emphasize that the proposed NIH Policy will apply to all NIH-supported interventional clinical trials, even if they do not fall under the requirements stated in the Notice of Proposed Rule Making.

Finally, the YODA Project agrees with the NIH that it would be helpful for any and all additional data elements to be required at the time of registration and results submission, and that these elements should align with each other for submission of registration and results. Through rigorous clinical trial policies set forth by the NIH in conjunction with the HHS, we can increase the availability and use of clinical research data to generate new knowledge that will benefit society.

On behalf of the Yale University Open Data Access (YODA) Project,

Joseph S. Ross, MD, MHS
General Internal Medicine, Yale University School of Medicine
Robert Wood Johnson Foundation Clinical Scholars Program
Center for Outcomes Research and Evaluation, Yale-New Haven Hospital
Health Policy and Management, Yale University School of Public Health
P.O. Box 208093
New Haven, CT 06520-8093
p: 203-737-7624; f: 203-737-3306

Yale University Open Data Access (YODA) Project Public Comment on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

The Yale University Open Data Access (YODA) Project at Yale University and the Yale-New Haven Hospital's Center for Outcomes Research and Evaluation (CORE) supports and applauds the draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information, expanding public availability of clinical trial summary results. While this is an important step forward in promoting the responsible and comprehensive dissemination of clinical research results, we believe that further steps can, and should, be taken to promote open science and share clinical research data.

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From: [Davis, Catherine \(Katie\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comment on Draft NIH Policy for Registration and Reporting of Results for NIH-funded Clinical Trials
Date: Friday, February 27, 2015 7:22:39 PM
Attachments: [image001.png](#)

Ladies and gentlemen,

This rule, while well-intentioned, would have **disastrous results for the science by discouraging investigators from conducting NIH-funded clinical trials**, particularly those at universities that have little research infrastructure (e.g. CTSA awards).

The process of registering a clinical trial is much too difficult with seriously inadequate support provided for investigators to navigate the process. As an obvious example, “Sponsor” means something completely different in this context than anywhere else, and there is no one to help you get it done. Most behavioral trialists will be unfamiliar with FDAAA and terms like “applicable clinical trial.” There should be a staffed CT.gov PRS support office with people to answer the phone to answer questions from investigators! Critiques from the Quality Assurance Review should come with a phone number for the person behind the email! Perhaps each NIH institute could have staff assigned to support PIs of new trials with the registration process. There should be much more extensive training available that is geared to NIH-funded investigator-initiated studies prior to instituting any such requirement/threat.

As an example, I had great difficulty registering my second trial, HL087923 (2008-2013), in ClinicalTrials.gov even when I knew the requirement and repeatedly tried to register it over years. My previous trial, DK060692 (2003-2008, NCT00108901) was registered timely because the NIDDK started the process by assigning me a userid (DavisC, NIDDK_DEM). When my funding shifted to NHLBI there was no apparent way for me to go about registering a new trial. Bizarrely, the userid that had been assigned to me by NIDDK would not permit me to register a trial funded by another institute. I also couldn’t obtain another userid for years – the process is very opaque and I think changed also during this time. Meanwhile I was worried that because the registration is required, I would get in trouble with NIH if I contacted my institute to get help with it.

Finally in 2014 I convinced my university’s administrative staff that they had to assign me a userid, and that I could not establish one on my own, which enabled me to register the trial (NCT02227095). **They didn’t even know that it was their job.** When I submitted the query to PRS, they were the ones named as being able to do so. This is probably not a unique situation given staff turnover, changing rules and shrinking research support resources at universities. My university administration (Dr. Michael Diamond, Senior VP of Research at Georgia Regents University) approved this statement:

“Dear Sir or Madam,

Dr. Catherine Davis, one of our university researchers, reports that she was unable to register her clinical trial (NIH R01 HL 087923) prior to enrolling subjects in 2008 due to difficulties with the ClinicalTrials.gov website. Dr. Davis had been assigned a ClinicalTrials.gov user id by the federal sponsor of a previous trial that she conducted. She reports that she was unable to use this id for a trial that had a different sponsor (NHLBI). Dr. Davis reports that she was independently unable to obtain a new user id as the website required this to be requested by her institution. Subsequently, Dr. Davis was assigned a new user id, entered all the website required trial information and responded to all website generated data queries. We appreciate your understanding of the difficulties encountered with the registration of this study.”

Other reasons:

1. Some types of data take much processing time before they are available for analysis.
2. Changes in the literature may necessitate reformulating the analysis or data processing approach late in the process.
3. The process of peer review can lead to major overhauls in analysis and presentation that improve the report—this can take years given review turnaround time (sometimes months) and multiple rejections (esp. for null or unexpected results). While this is the root of the problem the rule is meant to address, requiring investigators to post outcomes on a fixed timeline may produce misleading results that then hamper their ability to get published in quality journals.

Therefore I exhort you not to implement this rule until ClinicalTrials.gov has a major usability overhaul AND addressing the publication venues (journal editors). Perhaps having some way to downgrade a quality rating depending on how many of the trial results they publish are “expected” or “good news” – “hypothesis confirmation” vs. a closer-to-the truth rate of 50% or less trials with expected results, because **this is how we learn**. NLM could be charged with such a mission! A kind of “Trial Impact Truth Factor.”

Thank you for your attention. I would be happy to answer questions or assist in any way as this moves forward.

Yours,

Catherine L. Davis PhD FTOS
Professor of Pediatrics, Physiology & Graduate Studies
Georgia Prevention Institute, Medical College of Georgia
Georgia Regents University
Augusta, GA 30912
(706) 721-9551 direct
<http://gru.edu/institutes/gpi/davis.php>



On February 1, 2011, the Medical College of Georgia became Georgia Health Sciences University, with the medical school maintaining the name MCG. As of January 8, 2013, Georgia Health Sciences University is called Georgia Regents University.

From: [Seger, Yvette](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Seger, Yvette](#)
Subject: FASEB Comments on NOT-OD-15-019 (Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information)
Date: Wednesday, March 04, 2015 12:56:00 PM
Attachments: [FINAL FASEB Response to NIH CTgov Policy 20150304.pdf](#)

Dear NIH Clinical Research and Bioethics Policy Team,

Attached please find comments submitted on behalf of the Federation of American Societies for Experimental Biology (FASEB) regarding the draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information ([NOT-OD-15-019](#)). Please do not hesitate to contact me should you have any questions or require additional information.

Thank you for the opportunity to comment on this proposed policy.

Sincerely,

Yvette Seger

Yvette R. Seger, PhD
Director of Science Policy
Federation of American Societies for Experimental Biology
9650 Rockville Pike
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Office of Clinical Research and Bioethics Policy
Office of Science Policy, National Institutes of Health
6705 Rockledge Drive
Suite 750
Bethesda, MD 20892

March 4, 2015

Comments submitted via email: clinicaltrials.disseminationpolicy@mail.nih.gov

Dear NIH Clinical Research and Bioethics Policy Team,

The Federation of American Societies for Experimental Biology (FASEB) appreciates the opportunity to comment on the National Institutes of Health's (NIH's) draft Policy regarding dissemination of NIH-funded clinical trial information (NOT-OD-15-019). FASEB is composed of 27 scientific societies, collectively representing over 120,000 biological and biomedical researchers. The Federation recognizes the importance of transparent reporting for clinical trial information for the medical, research, and patient communities, and we applaud the efforts of NIH and the National Library of Medicine (NLM) to develop the ClinicalTrials.gov website into a robust resource. Sharing information about clinical trials, including high-level demographics of the subject population and summary results, can help the scientific community avoid unnecessary duplication of studies and increase detection of adverse events across trials. Despite these major social benefits, FASEB has several concerns about the draft Policy, some of which were also articulated in our [comments](#) in response to the Department of Health and Human Services's (HHS's) Notice of Proposed Rulemaking (NPRM) "Clinical Trials Registration and Results Submission."

The proposed Policy would require registration and results reporting for all NIH-funded clinical trials on ClinicalTrials.gov. Some NIH-funded clinical trials are already subject to these requirements through Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). These trials include controlled, interventional studies of drugs, biological products and devices regulated by the Food and Drug Administration (FDA). FDAAA excludes phase 1 trials, which represent initial assessments of drug or device safety and aid in determining appropriate dosage and potential side-effects. The proposed NIH Policy, however, would require registration and reporting of all NIH-funded clinical trials, including phase 1. While this would certainly increase the amount of information available to patients, clinicians, and researchers through ClinicalTrials.gov, we are concerned about several potential unintended consequences associated with posting the results of early stage clinical assessments in such a public forum. Therefore FASEB recommends that NIH A) exclude Phase 1 clinical trials from this Policy or B) limit data reporting for Phase 1 clinical trials to adverse events.

Reporting results from Phase 1 clinical trials may lead to premature interpretation of outcomes

Much of the proposed Policy is focused on improving reporting and communication of clinical trial information to the public. FASEB believes that posting accurate data from trials that assess efficacy (e.g., Phase 2 or 3) provides more utility to patients and physicians. However, mandatory reporting of Phase 1 clinical trials – which, are by nature assessments of safety rather than efficacy – could mislead clinicians and patients, inadvertently reducing patient safety.

If not implemented in a manner that ensures appropriate financial and staffing resources, the proposed substantial changes could result in large volumes of data with low utility for both the scientific community and the public

One of FASEB's greatest concerns is the capability of NLM to receive, store, and process clinical trial data assuming full compliance for both the HHS proposed rule and NIH Policy. The proposed rule and the draft NIH companion policy expand the types of clinical trial types required to register and report data to ClinicalTrials.gov and will increase substantially the volume and frequency of data uploaded to the database. Similarly, although Title VIII of FDAAA already provides enforcement actions for non-compliance, we anticipate that increased awareness of these provisions will increase vigilance of institutions and investigators to report clinical trial data. Therefore, it is critical that HHS and NLM ensure that existing resources – both digital and human – are capable of managing high volume data uploads, customer service requests, and enforcement procedures prior to full implementation of the proposed policy or proceeding with enforcement actions.

FASEB appreciates the opportunity to provide comments on this proposed rule. The efforts of NIH and NLM to develop ClinicalTrials.gov into a robust information source for clinicians, patients, and researchers are commendable and the proposed rule would build upon this success. However, we encourage NIH to address the concerns outlined in this letter prior to finalizing and implementing this Policy.

Sincerely,

A handwritten signature in black ink, appearing to read "Joseph R. Haywood". The signature is fluid and cursive, with a large, sweeping flourish at the end.

Joseph R. Haywood, PhD
FASEB President

From: [Joel MacAuslan](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comment on proposed Trials policy
Date: Friday, March 06, 2015 12:46:27 AM

To Whom It May Concern:

It is not clear what unaddressed, underlying problem the proposed change of policy is intended to address. However, the proposed rule based on prospective assignment of subjects, with even small NIH funding, seems extraordinarily heavy-handed. It apparently has no exceptions whatsoever, nor even lighter-weight accommodations for any class or size of trials involving prospective assignment. It suggests a mindset that clinical research is only conducted in very large organizations.

By way of example, consider the finding that singing is (for many people) a way to overcome stuttering. If a lone practitioner had attempted to determine this under the new rule, it appears that s/he could not conduct a small study on an NIH grant with a few subjects prospectively assigned to a treatment group and a control group, without incurring the overhead of full registration and reporting through ClinicalTrials.gov.

Similar comments apply to Dr. Lorraine Ramig's finding that many Parkinson's Disease patients can greatly improve their speech by "thinking loud". (This is the basis of Ramig's Lee Silverman Voice Therapy.) This could begin with a lightweight project requiring no special staffing or reporting. But no longer, if the project were covered under the new rule.

This proposed rule apparently reflects NIH's stereotyped mindset that research is conducted by large, bureaucratic, heavily staffed organizations.

It presupposes a staffer who is already familiar with ClinicalTrials.gov, or can quickly become so across the many projects that s/he is presumed to staff. So perhaps the extra work of compliance is assumed to be small. The additional training for compliance with this rule is assumed to be spread across many projects, for the specialized staffers who focus on clinical-trial management.

But that is simply not the world that small organizations live in. There ARE no such staffers! (For example, the median size of organizations receiving SBIR/STTR grants is 10 employees.) Instead, that management is an additional duty of the PI or his/her lone assistant, a person whose "day job" focuses on far broader duties than compliance with ClinicalTrials.gov. S/he may run a clinical trial at most once every 2-3 years. The overhead of additional training and compliance is therefore a substantial burden for a single project.

Indeed, "very few" may be the key: This rule will have the effect of steering such PIs *completely away* from trials that involve any prospective assignment on NIH-funded projects. However slight you may imagine the training and compliance burden for a covered project, it will likely be much greater than the PI's effort to find a different project, one that avoids the new rule. The original project will not be conducted at all.

That is definitely the lesson that I expect to draw. I have a great many responsibilities. Adding ones related to ClinicalTrials.gov merely because of this new rule will almost certainly be an irresponsible use of my time. In particular, it will be far less efficient of my time than abandoning a planned trial in favor of some other activity that does not run afoul of this proposed rule. The planned trial will be lost.

-Joel MacAuslan, PhD
Chief Scientist

STAR Analytical Services / Speech Technology & Applied Research Corp.
Bedford, MA 01730
v: 781-861-STAR (7827) f: 800-230-8572
<http://www.STARAnalyticalServices.com>

From: [Thornicroft, Graham](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Pringle, Beverly \(NIH/NIMH\) \[E\]](#); [Lara Fairall](#); [Inge Petersen](#)
Subject: RE: NIH Request for Public Comments on Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
Date: Friday, March 06, 2015 4:10:04 AM

Dear sir/madam

As a co-PI for the NIH funded COBALT trial I am pleased to comment on these proposals

1. I support the principles as set out
2. It is clearly right that the public funds spend on such trials should lead to publically available information to support better health
3. It is right that all trials should be registered in a way that is openly available to the public
4. Yet putting the main findings in the trial register may compromise such results from being published in peer reviewed journals as some journals will need accept data that have been 'previously published'
5. NIH will clearly want full results of its funded trials in the public domain as soon as possible- yet delays can occur for several reasons- including those which are attributed to the authors or the journals or both eg it quite often happens, even for the first journal receiving a paper, that their peer review process can take 12-18 months in total, and if the paper goes to a second or third journal these delays concatenate
6. It is better if registration at the trials website is completed before the recruitment of the first participant

I hope that these comments may be helpful to you

best wishes

graham thornicroft

@ThornicroftG on Twitter

Act now to support the inclusion of a strong mental health component in the UN Sustainable Development Goals: see the www.FundaMentalSDG.org

Contact:

NB: please send email to me at graham.thornicroft@kcl.ac.uk

Or contact me via jenny agha at:

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From: Pringle, Beverly (NIH/NIMH) [E] [mailto:bpringle@mail.nih.gov]

Sent: 03 March 2015 17:26

To: 'Ali, Mohammed K'; 'muthoni mathai' (mathai@web.de); 'Prof. David M. Ndeti (dmndetei@uonbi.ac.ke)'; 'Becker, Anne Edith'; 'Betancourt, Theresa S (tstichic@hsph.harvard.edu)'; 'Ashok Malla (Ashok.Malla@douglas.mcgill.ca)'; Cohen, Alexis (ACF) (CTR); 'Ekstrand, Maria (Maria.Ekstrand@ucsf.edu)'; 'MARY SMITH FAWZI'; Thornicroft, Graham; 'Yangfeng Wu (ywu@georgeinstitute.org.cn)'; 'mamahd@psychiatry.wustl.edu'; 'Joy Noel Baumgartner (joy.baumgartner@duke.edu)'; 'Conwell, Yeates (Yeates_Conwell@URMC.Rochester.edu)'; 'Huang, Keng-Yen (Keng-Yen.Huang@nyumc.org)'; 'Milton Wainberg'; 'Judy Bass (jbass1@jhu.edu)'; 'Maria oquendo'; 'Sylvia Kaaya'; 'Brandon Kohrt, Ph.D. (brandon.kohrt@duke.edu)'; 'Bahr Weiss (bahr.weiss@gmail.com)'; 'Tol, Wietse'; 'Wissow, Lawrence'; 'Laura Murray (lmurra15@jhu.edu)'; 'Meffert, Susan (Susan.Meffert@ucsf.edu)'; 'Mark Gluck (gluck@pavlov.rutgers.edu)'; 'De Erasquin, Gabriel A. (gdeeraus@health.usf.edu)'; 'guilhermelgborges@gmail.com'

Subject: NIH Request for Public Comments on Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

Dear Colleagues,

For Your Information: The NIH has extended the public comment period for commenting on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information to March 23, 2015. Given your experiences as PIs on a non-U.S. based clinical trials and as leaders of a non-pharmaceutical treatment trials, you might be interested in responding. I know that your perspectives will make a valuable contribution. Here is the link to the request for public comment.

[NOT-OD-15-019 "NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information"](#)

Thanks, Beverly

From: Pringle, Beverly (NIH/NIMH) [E]

Sent: Friday, February 27, 2015 11:54 AM

To: Ali, Mohammed K; 'muthoni mathai' (mathai@web.de); Prof. David M. Ndeti (dmndetei@uonbi.ac.ke); 'Becker, Anne Edith'; Betancourt, Theresa S (tstichic@hsph.harvard.edu); Ashok Malla (Ashok.Malla@douglas.mcgill.ca); Cohen, Alexis (ACF) (CTR); Ekstrand, Maria (Maria.Ekstrand@ucsf.edu); MARY SMITH FAWZI; Thornicroft, Graham (graham.thornicroft@kcl.ac.uk); Yangfeng Wu (ywu@georgeinstitute.org.cn); 'mamahd@psychiatry.wustl.edu'; Joy Noel Baumgartner (joy.baumgartner@duke.edu); Conwell, Yeates (Yeates_Conwell@URMC.Rochester.edu); Huang, Keng-Yen (Keng-Yen.Huang@nyumc.org); Milton Wainberg; Judy Bass (jbass1@jhu.edu); Maria oquendo;

Sylvia Kaaya; Brandon Kohrt, Ph.D. (brandon.kohrt@duke.edu); Bahr Weiss (bahr.weiss@gmail.com); Tol, Wietse; Wissow, Lawrence; Laura Murray (lmurra15@jhu.edu); Meffert, Susan (Susan.Meffert@ucsf.edu); Mark Gluck (gluck@pavlov.rutgers.edu); De Erausquin, Gabriel A. (gdeeraus@health.usf.edu); guilhermelgborges@gmail.com

Subject: Funding Opportunity Announcement calling for proposals for 1-year administrative supplements

I am writing to alert you to a newly-posted Funding Opportunity Announcement calling for proposals for **1-year administrative supplements** in targeted areas of mental health science.

The link to the FOA is: <http://grants.nih.gov/grants/guide/pa-files/PA-15-128.html>

Key information:

Submission due date is June 1, 2015

Supplements can request only 1-year funds

Applicants must specify which topic area they are responding to

Applicants must describe how the proposed work is within scope of the parent award.

Please let me know if you have any questions.

All the best,

Beverly

~~~~~

**Beverly Pringle, PhD**

Chief, Global Mental Health Research

Office for Research on Disparities & Global Mental Health

National Institute of Mental Health

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E-mail: [bpringle@mail.nih.gov](mailto:bpringle@mail.nih.gov)

Desk Phone: 301-443-3725

Telework Phone: 202-543-8283

~~~~~

GRAND CHALLENGES IN GLOBAL MENTAL HEALTH

<http://grandchallengesgmh.nimh.nih.gov/>

<http://grandchallengesgmh.nimh.nih.gov/Grand%20Challenges%20in%20Global%20Mental%20Health.pdf>

From: janiceg671@aol.com
To: clinicaltrials.disseminationpolicy
Subject: comments on Draft NIH Policy for Registration and Reporting of Results of NIH-funded Clinical Trials
Date: Wednesday, March 18, 2015 8:55:10 PM

This proposed policy greatly expands the number of trials that an institution would need to oversee and ensure that investigators complete. The NIH is currently proposing in an NPRM to expand the data elements that would be required to be submitted, which will already put an increased burden on institutions but with this added proposed requirement it would greatly expand the number of clinical trials that would need to be registered.

It does not appear that those proposing this requirement are aware of the intense time requirements to get through the antiquated CT.gov registration system to register, update and then submit results. This is a huge unfunded mandate.

As you are aware, a 1991 revision to OMB Circular A-21 instituted a cap on the administrative portion of the F&A rate at 26 percent, which includes General Administration, Departmental administrative costs, and Sponsored Projects Administration. New compliance requirements mandated by the federal government since 1991 have meant the 26-percent administrative cap already prevents universities from recovering the full administrative costs of research. More than 90 percent of all research institutions and universities spend more on administration and regulatory compliance than is reimbursed under a 26-percent cap. Studies suggest that the actual administrative rate at most universities is close to 30 percent, which means that institutions are already subsidizing the difference.

Currently, with just the requirements under FDAAA it takes between .25 and .5 FTE to administer the CT.gov registration for around 100 clinical trials. Since this proposed policy greatly expands the definition of trials that would need to be added to CT.gov, additional staff requirements would be required yet the institution would not receive any more funding to offset this mandate. It seems that if this issue were so important, there should be funding to the institution to support this potential new requirement.

Unfortunately, this appears to be another expensive unfunded mandate with very questionable benefit. Most NIH sponsored investigators main goal is publication so the arguments made in favor of registration such as non-publication of some studies does not seem to apply in this case. Therefore, there does not appear to be any reasonable reason to require another unfunded mandate of an institution. Some studies have already shown that investigators spend 40% of their time on administrative work and not on research and this is another example of huge amounts of administrative time requirements on already overworked investigators.

This proposed definition of a clinical trial is significantly different from clinicaltrials.gov requirements. It appears that a study would need to be registered even if only one person was enrolled in one arm of the study. How can any valid data be obtained with a sample size of one? Why would results need to be put in? This makes no sense.

The current status of the CT.gov system is that it is very user unfriendly and is very difficult for our investigators as well as administrative staff to use. Since we use this system regularly and work with our investigators there are multiples of negative comments that we receive about the clinicaltrials.gov system and how even departments of physicians cannot figure out what the system is asking for. It took a qualified staff member about a year of working with the system to get a degree of comfort with adding the information in the required format. To

expect already busy investigators figure out this system is unreasonable, to say the least. One physician who has been trying to enter results for quite some time finally gave up. He stated "This system is a piece of crap." Please consider making the system user friendly to investigators before making it mandatory for every possible type of clinical trial.

Please continue to make the requirements the same as FDAAA so that we do not have to have different definitions based on funding source. As you may know, many investigators get funding from various sources and exactly which funds are involved in a newly defined clinical trial would greatly add to the complexities of our current systems capabilities.

NIH already requires making publications publically available for NIH sponsored research. This new requirement would be redundant in many cases. Also, because the definition of clinical trial is so broad, the results from study to study would not be comparable. Another downfall of this broad inclusion criteria is that non-peer reviewed data would be entered into CT.gov. It would be very bad policy if bad data were required to be entered into a database with very valid data, since it would be impossible to distinguish the two and invalid data could be used inappropriately.

Please keep the reporting requirements as they currently stand and do not add another unnecessary burden and unfunded mandate on our already over-burdened researchers.

Thank you for your consideration.

From: [Norton,Jane-Ann D](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Wimsett,Gary D,JR](#)
Subject: Notice Number: NOT-OD-15-019
Date: Thursday, March 19, 2015 3:27:29 PM
Attachments: [NIH comments March 2015 Final.pdf](#)

To Whom It May Concern:

Please find attached the comments from the University of Florida in regards to the "NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" Notice Number: NOT-OD-15-019.

Notice Number:

NOT-OD-15-019

Key Dates

Release Date: November 19, 2014

Response Date: New Date March 23, 2015 per issuance of [NOT-OD-15-068](#). (Original Date: February 19, 2015)

Issued by

National Institutes of Health ([NIH](#))

Kind Regards,

Jane-Ann

Jane-Ann Norton, B.S.
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Advance Notice: NONE

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Draft NIH Policy Section	General comments/thoughts
<p>links</p> <p>http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html</p> <p>http://www.icmje.org</p>	<p>We believe there is an ethical responsibility inherent in registration and results reporting and we believe that fulfilling this responsibility is good practice and science. Our comments on the proposed NIH Policy are intended to highlight the additional and significant administrative burdens placed on Academic Medical Centers in hopes that these impacts might be minimized. We understand and support the mission of the NIH to advance research results into knowledge, products, and procedures that improve human health.</p> <p>Academic Medical Centers (AMC) and researchers would like to state that the compliance burden regarding this new policy applies disproportionately to individual investigators who do not have dedicated personal to assist them.</p> <p>PRS administrators in academic medical centers often oversee many hundreds of records. Currently, administrators’ effectiveness is hampered by the limitations of the ClinicalTrials.gov PRS system, most notably the inability to sort, filter, or generate reports using any fields in the records of the institutional account. If PRS administrators in Academic Medical Centers are to perform their important job functions at a high level, they need better tools and reasonable system design changes that facilitate registration and results reporting for our scientists and their study teams. This is particularly true in light of this proposed NIH policy change which will significantly increase the volume of studies that need to be registered in the database.</p>
<p>Draft NIH Policy for Registration and Reporting of Results for NIH-funded Clinical Trials</p> <p>This Policy applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the FDAAA registration and results submission requirements set forth in Section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)). For purposes of this Policy, a clinical trial is defined as “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.</p>	<p>At Academic Medical Centers the study is initiated and run by the principal investigator, in the event of death or relocation, could the sponsor submit a permanent waiver for results requirements? Can the record be closed from the institutional account and posted on the public site with a notice of the reason that the study was terminated and only partial results (if any) were obtained? These situations cause an enormous burden on institutional resources. Much time is spent attempting to locate data and composing language that satisfies PRS reviewers, but the posted information often does not provide benefit to the public or the scientific community. Considerable PRS reviewers’ time is also spent guiding us through the process.</p>

Draft NIH Policy for Registration and Reporting of Results for NIH-funded Clinical Trials

Effective Date

We would suggest that the Effective Date would be the date of the policy approval going forward. This would lessen the burden to academic medical centers and investigators.

From: [porourke](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comments for submission
Date: Friday, March 20, 2015 3:25:35 PM
Attachments: [NIH Draft Policy.pdf](#)

Thank you for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019)*. I am writing on behalf of Partners Healthcare in Boston, MA. Please see uploaded document.

Pearl O'Rourke

P. Pearl O'Rourke, MD
Director, Human Research Affairs
Director, ESCRO
Partners HealthCare
Boston, MA
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Boston, MA 02116
617 424-4152

The information in this e-mail is intended only for the person to whom it is addressed. If you believe this e-mail was sent to you in error and the e-mail contains patient information, please contact the Partners Compliance HelpLine at <http://www.partners.org/complianceline> . If the e-mail was sent to you in error but does not contain patient information, please contact the sender and properly dispose of the e-mail.



P. Pead O'Rourke, M.D.
Direc/01; H1111n11Research Affairs

March 19, 2015

RE: NOT-OD-15-019: NIH Draft Policy on Clinical Trials Registration and Results Reporting

Thank you very much for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019)*. I am writing on behalf of Partners HealthCare System (Partners) which provides financial, administrative, and centralized IRB oversight of research grants and clinical trials awarded to the Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH), and McLean Hospital (McLean). The Spaulding Rehabilitation Hospital (SRH) is also a Partners hospital but with its own research administration and IRB oversight. Partners is one of the nation's leading non-profit biomedical research organizations; its hospitals are the principal teaching affiliates of Harvard Medical School. In FY 2014, Partners hospitals received approximately \$700 million in federal funding, primarily from the NIH, to support basic and clinical research, including drug, device and behavioral trials. There are over 1700 ClinicalTrials.gov records within the Partners hospitals' organizational accounts.

While we support the NIH's expectations and efforts to make research and results information publicly available, we are concerned that the proposed policy without clarification and revision would impose a significant administrative burden on investigators and institutions and lead to confusion over interpretation of requirements. Thus, based on our experience administering a large and diverse clinical trials research program and meeting current clinical trials registration and results reporting requirements, we respectfully offer recommendations we believe would assist the NIH in developing a clear and coherent policy.

Research Management

NIH Definition of clinical trial and the effect on registration and reporting requirements

We acknowledge NIH's new definition of clinical trial to determine whether a NIH funded clinical trial requires registration and results reporting. We appreciate that NIH has elaborated on certain terms within the definition (e.g. 'prospectively assigned', 'intervention') and published FAQs and case studies. Of note, we find the case studies particularly helpful and would welcome publication of additional case studies over time.

However, it is important to recognize that when the NIH policy and the simultaneously issued FDAAA NPRM become effective, investigators conducting PHinitiated research will need to navigate four different clinical trial definitions and registration criteria: the FDAAA definition of Applicable Clinical Trial, the NIH definition of clinical trial, the ICMJE definition of clinical trial, and the CMS definition of qualifying clinical trial. These definitions of clinical trial each differ or appear to differ from one another, in some cases in subtle ways; the associated timelines for registration and overall responsibilities (results reporting, updating the record) differ across some (but not all) of these sources of rules. In our experience, investigators are frequently confused by these various requirements and a good deal of effort and resources are required to assist them in understanding their responsibilities.

In order to support institutions and investigators in understanding and reconciling the various definitions and requirements, we strongly recommend that the NIH collaborate with FDA, ICMJE and CMS to harmonize definitions to reduce or eliminate differences. If this is not possible, we recommend a joint effort to publish guidance comparing and contrasting all requirements for clinical trials registration and results reporting. Differences in definitions should be explicitly articulated and highlighted with case studies.

Clarity with regards to privately funded studies using NIH Infrastructure

The Scope and Applicability section of the proposed NIH policy asserts that the policy'... applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the FDAAA registration and results submission requirements set forth in Section 402(j) of the Public Health Service Act (42 U.S.C. 2820)).'

We suggest clarification regarding privately funded studies using NIH infrastructure. We note that National Cancer Institute Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials (Notice Number: NOT-CA-15-001, release date 1/28/15) defines *NCI-Supported Clinical Trials* as follows: '...all clinical trials financially supported - whether in whole or in part - by the NCI. Clinical trials that are wholly funded by private entities (and in which the data from the clinical trial belong to the private funder) are not considered to be NCI-supported even if such studies are conducted at the NCI-designated Cancer Centers and benefit from the Cancer Center infrastructure.'

The clarification that privately funded trials using NCI supported infrastructure are not covered as part of the NCI policy is a significant detail that helps academic centers understand the scope of the policy. Clinical and Translational Science Awards (CTSA) set up infrastructure at academic institutions similar to the NCI-designated Cancer Centers. We request the Scope and Applicability section of the proposed NIH policy insert similar language which provides helpful clarity regarding privately funded studies using CTSA infrastructure.

Required results reporting for behavioral clinical trials

We appreciate that the ClinicalTrials.gov database has undergone many revisions to accommodate different types of research including behavioral and observational research. The NIH proposed policy to require results reporting of behavioral clinical trials will now include investigators who have no experience with the results database. We note that ClinicalTrials.gov has examples of studies for results data entry (parallel study design, cross-over study design, etc). These examples have been very helpful to the academic research community. We recommend that NIH, in collaboration with ClinicalTrials.gov, publish additional examples specific to behavioral study design.

Compliance with policy

The NIH draft policy does not provide specific information on certain key aspects of implementation that may be confusing to investigators. We recommend the following processes be clarified prior to the effective date of the final policy:

1. *Determination of whether a project meets the NIH definition of clinical trial:* The NIH FAQ, FDAAA- Further Resources for NIH Grantees (<http://grants.nih.gov/clinicaltrials/fdaaa/faq.htm#832>) indicates that 'investigators and institutional officials ... are encouraged to work together to determine whether or not an NIH grant is supporting an applicable clinical trial, and whether or not that trial must be registered under FDAAA. This determination is communicated to the NIH in the grantee's certification of compliance with FDAAA.' If the investigator/Institution makes a decision as to whether research qualifies as a clinical trial under this policy and NIH disagrees, how will this be communicated to the investigator/institution? Through the Notice of Grant Award? Who has final authority to make the determination regarding whether a study meets clinical trial definition? The NIH or the grantee institution?
2. *Effective Date:* The draft indicates the policy is effective for competing grant applications and, contract proposals submitted, received, or initiated after the effective date. We recommend that NIH provide further clarity regarding the applicability of the policy, if any, to noncompeting NIH supported clinical trials as of the effective date. Specifically, please clarify if results reporting will be required for

- a. A clinical trial in which the primary completion date is reached shortly *after* the effective date;
 - b. A clinical trial in which the primary completion date is reached shortly *before* the effective date;
3. *Direct charging FDAAA compliance costs to NIH grants:* The NIH FAQ, FDAAA - Further Resources for NIH Grantees (http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#836) states that the cost of FDAAA compliance will generally be allowable as a direct charge to NIH supported grants. We recommend that the NIH provide examples of allowable costs) for registration and results reporting efforts, e.g., whether biostatistician support and data entry costs are allowable and approximate expectations for registration and results data entry.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification.



P. Pearl O'Rourke, MD
Director, Human Research Affairs
Partners Healthcare
116 Huntington Ave., Suite 1033
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From: [Cocanougher, Denise](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Response to NIH Policy
Date: Friday, March 20, 2015 4:06:00 PM

Thank you for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019.)* I am writing on behalf of the Brigham and Women's Hospital (BWH). Please see attached document.

Thank you.

Paul J. Anderson, MD, PhD

Chief Academic Officer & Senior Vice President of Research
K. Frank Austen Professor of Medicine, Harvard Medical School
Brigham and Women's Hospital
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Tel: 617.732.8990 | Fax: 617.732.5343 |

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From: [Robertson, Stacey](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comments for Docket No NIH-2011- 0003 and RIN 0925-AA52 & Notice Number NOT-OD-15-019
Date: Friday, March 20, 2015 4:52:15 PM
Attachments: [3 20 2015 AdvaMed comments on NIH-2011- 0003 NPRM CT.gov comments.pdf](#)

Dear Sir/Madam:

Please see the attached comments pertaining to the National Institutes of Health (NIH) Proposed Rule and Request for Comments on Clinical Trials Registration and Results Submission and the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

(Docket No. NIH-2011- 0003 and RIN 0925-AA52; Clinical Trials Registration and Results Submission; Proposed Rule; Request for Comments AND Notice Number NOT-OD-15-019: NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information)

For questions or additional information, please contact Tara Federici, Vice President, Technology and Regulatory Affairs, AdvaMed
via phone: 202/ 434-7208 or E-mail: tfederici@advamed.org.

*Stacey Robertson (Assistant to Khatereh Calleja / Ruey Dempsey / Tara Federici)
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March 20, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. NIH-2011- 0003 and RIN 0925-AA52; Clinical Trials Registration and Results Submission; Proposed Rule; Request for Comments

And

Notice Number NOT-OD-15-019: NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

Dear Sir or Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the National Institutes of Health (NIH) Proposed Rule and Request for Comments on Clinical Trials Registration and Results Submission and the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

The Advanced Medical Technology Association (AdvaMed) is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

We understand that the proposed rule provides for an expanded registry and results data bank and is intended to be responsive to 402(j)(3)(D) of Title VIII of the Food and Drug Administration Amendments of 2007 (FDAAA). We also understand that the NIH intends to require all NIH-funded device clinical trials to register and submit summary results whether they are funded in whole or in part by NIH per Notice Number NOT-OD-15-019.



AdvaMed has both general and specific comments below. Please note that our general and specific comments below also apply to device clinical trials that may be funded in part by a grant from NIH but where the responsible party has ownership of trade secret or confidential commercial or financial information.

GENERAL COMMENTS

Disclosure of Proprietary and Confidential Commercial Information

AdvaMed supports clinical trial registration of applicable device trials and reasonable disclosure of device trial results to ensure patient and clinician access to important information about the health benefits and risks of medical devices. However, we are gravely concerned about NIH's proposal to require the submission of results information for applicable clinical trials of devices that are not approved, licensed, or cleared for any indication (regardless of whether the sponsor seeks approval, licensure, or clearance) as well as other proposals in the rule which will disclose or may have the effect of disclosing proprietary, confidential data (e.g., detailed intervention descriptions and NIH consideration of whether or not to disclose the full protocol).

The final rule must strike an appropriate balance between transparency on the one hand and protections for the proprietary and confidential device intellectual property and trade secrets that underline device innovation on the other. We believe the disclosure of proprietary, confidential clinical trial data associated with products which are not approved, licensed or cleared or other such disclosures of proprietary confidential information will chill interest in developing new and innovative devices in the U.S. Companies and venture capital firms will be reluctant to fund device development in the U.S. if disclosure of clinical trial information enables competitors to shortcut research and development for competing products.

Unlike the drug industry where entire molecules are patented and are frequently patented even before the first clinical trial begins, patents¹ provide little protection in the device industry. Competitors can easily negate device patents with simple engineering or design changes. This lack of patent protection explains the rationale for the statutory ban in the U.S. on the disclosure of any information related to an investigational device exemption (IDE) including even the existence of the IDE until the device has been approved by FDA. Additionally, because of the iterative nature of device innovation, the average life-cycle for many devices may be as short as 18 months. In many instances, relatively small populations receive each generation of the device. As a result, device companies may have a small market and a relatively short time from which to recoup the resources spent on the conduct of a clinical trial. In short, developing innovative technology requires a great deal of time and a large capital investment. If a company or investor cannot achieve a fair return on investment, interest in pursuing device innovation will diminish. Making clinical trial information available to potential competitors will minimize the time and investment it will take for competitors to develop and market a similar device.

¹ Medical device manufacturers do pursue patents on their products. However, due to the relative ease with which engineering changes can be made to design around device patents, patents do not play the same strong role of protecting intellectual property that they play in the development of drugs, for example.

Small device companies (sales of less than \$100 million) account for a vast number of device innovations and contribute greatly to maintaining strong price competitiveness across the industry (nearly 70 percent of AdvaMed's members are small companies). In many instances, small companies are willing to invest in developing technologies for niche, pediatric and orphan markets – patient communities that may otherwise be overlooked and underserved. Disclosure of proprietary, confidential clinical trial information may, in particular, disadvantage small device companies or have the unintended consequence of eliminating many small device companies from the marketplace and have a corresponding negative, long-term impact on patient access to innovative technologies.

For these reasons and as discussed in more detail in our specific comments, the final rule must appropriately allow for delayed disclosure of applicable device trials to account for situations where product development efforts (including clinical trials) may be delayed, put on hold or reprioritized due to funding issues or other business reasons. Further, companies often have intentions to continue product development and subsequent pursuit of device approval or clearance even after receiving an initial non-approval or not substantially equivalent finding from FDA. The final rule should only require disclosure of device trial results where companies have affirmatively declared they have abandoned development of the product. In addition, as described in more detail below, in order to promote continued device innovation in the U.S., the rule should not require disclosure of the full clinical trial protocol.

Standardized Terms and Definitions

Although we understand and are supportive of NIH's desire to utilize standardized terms and definitions in the clinical trial registry and results data bank, in general, there is a need for more flexibility in the ClinicalTrials.gov database. Some of the proposed data elements are more appropriately directed toward drug trials and are difficult for device trials to complete (e.g., the proposed adverse event requirements by organ system). Submissions should rely on standardized terms when appropriate but all data elements should allow for the "other" category with an opportunity to describe unlisted data elements so as to appropriately and accurately describe trial information.

Encouraging Voluntary Submissions to ClinicalTrials.gov

Companies that would otherwise voluntarily submit clinical trials to ClinicalTrials.gov may forego the opportunity given the detailed, burdensome requirements and the associated overly aggressive timelines of ClinicalTrials.gov in this proposed rule. We believe NIH should scrutinize the ClinicalTrials.gov requirements and their corresponding reporting timelines to assess which data elements are essential in order to encourage voluntary registration of more trials that do not meet the "applicable" trial definition.

Delayed Disclosure

We are concerned that the proposed rule repeatedly interprets existing legal requirements (i.e., Federal Food Drug and Cosmetic Act and the Public Health Service Act) in such a way as to severely limit or undermine use of the device delayed disclosure provision in 402(j)(2)(D)(ii)(I) of the PHS Act – a provision that was added to FDAAA and which passed Congress with strong bi-partisan support. For example, NIH's extraordinary interpretation of the Federal Food Drug

and Cosmetic Act (FD&C Act) allows NIH to treat all trials for 510(k)s as trials for “new” uses (as opposed to initial uses) and to treat all combination products as applicable drug trials under the proposed rule in an apparent effort to deny the PHS Act’s statutory protection of delayed disclosure to device products.

We also want to note for the record that AdvaMed provided extensive written comments in June 2009 to the National Institutes of Health’s request for comments on the expansion of the clinical trial registry and results data bank that we have attached to these comments. We are resubmitting them here because we believe they remain helpful in developing the final rule.

Specific Comments

AdvaMed’s specific comments follow below. All page references are to the pre-publication version of the NPRM with the exception of the first comment which references the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. We attempt to identify relevant page numbers and the relevant portions of the proposed rule in the pre-publication version of the NPRM where possible but given the length, complexity and repeated descriptions of various aspects of the rule throughout the proposed rule, we were unable to reference all applicable page numbers and changes to the regulation in every instance.

Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information – “This Policy applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the FDAAA registration and results submission requirements set forth in Section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)).”

Comment

402(j)(5)(A)(i) of the Public Health Service (PHS) Act required NIH to certify that “if an applicable trial is funded in whole *or in part* [emphasis added] by a grant from any agency of the Department of Health and Human Services, including the Food and Drug Administration, the National Institutes of Health, or the Agency for Healthcare Research and Quality, any grant or progress reports forms required under such grant shall include a certification that the responsible party *has made all required submissions under paragraphs (2) and (3)* [emphasis added] before releasing any remaining funding for a grant or funding for a future grant to such grantee.”

From this, it is clear that Congress intended that device delayed disclosure and other elements of Title VIII of FDAAA would apply to federally funded studies whether they were funded in whole or in part. As noted in our comments below, NIH does not have authority to exceed the scope of disclosure permitted under the FD&C Act or under the FDA’s regulations to disclose trade secret or confidential commercial or financial information associated with device clinical trials that may be funded in part by a grant from NIH (including funding through SBIRs and STTRs) where the responsible party has ownership of certain trade secret or confidential commercial or financial information.

In contrast, where the federal government or NIH has wholly funded research, development and a product's associated clinical trials, we believe NIH has authority to disclose and should disclose all information.

Submission of non-technical and technical summaries of results – we invite further public comment on methods we might employ to help answer this question [whether narrative summaries can be provided in a manner that is objective and not misleading] so that we can explore this issue more thoroughly before making a final determination. Pages 61 – 64 and elsewhere, and related proposed rule provisions.

Comment

AdvaMed provided detailed recommendations on this question (which we will not repeat here) in our June 2009 comments to NIH (see attached). In order to make ClinicalTrials.gov as helpful as possible for the lay audience – for which the database was largely created – we recommend that NIH rapidly develop a template for narrative non-technical summaries. Although not to be ignored, concerns that narrative non-technical summaries may be misleading can be addressed via added disclaimers that a narrative summary may not be able to adequately capture important details about the trial; patients should thoroughly review the ClinicalTrials.gov database information and the linked Summary of Safety and Effectiveness Data (SSED) and/or 510(k) Summary; and patients should discuss any questions they have with their health care practitioner.

We invite public comment on whether the registration and results information that is proposed for submission in this NPRM is sufficient to meet the statutory requirement in section 402(j)(3)(D)(iii)(III) of the PHS Act to provide “information on the protocol” as may be necessary to help evaluate the results of the clinical trial or whether submission of additional information, including submission of the full protocol, should be required. Pages 65, 66 and elsewhere, and related proposed rule provisions.

And

For which applicable clinical trials must results information be submitted? – §11.42 – Proposed §11.42 identifies the applicable clinical trials for which results information must be submitted to ClinicalTrials.gov, according to this proposed rule unless the requirement is waived under proposed §11.54..... For reasons described in section III.C.5 of this preamble, we also propose to require the submission of results information for specified applicable clinical trials of drugs or devices that are not approved, licensed, or cleared for any indication (regardless of whether the sponsor seeks approval, licensure, or clearance). This proposal is consistent with the requirement in section 402(j)(3)(D)(ii)(II) of the PHS Act that the Secretary establish through regulation whether or not results information must be submitted for applicable clinical trials of drugs and devices that have not been approved, licensed, or cleared by FDA, whether or not approval, licensure, or clearance is sought. Pages 247, 248, 413 and elsewhere, and related proposed rule provisions.

And

§11.48(a)(6) – Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared devices. Page 430 and elsewhere, and related proposed rule provisions.

Comment

We do not support providing full protocols for approved, cleared or for unapproved, unlicensed, or uncleared products, or the disclosure of summaries that effectively compromise the confidentiality of such protocols. We also do not support inclusion of clinical trial results information for applicable trials of unapproved, unlicensed or uncleared devices. We believe disclosure in the ClinicalTrials.gov database should not exceed the scope of disclosure permitted under the FD&C Act and the FDA's regulations for any number of reasons, including protecting incentives for companies and individuals to develop devices that the public needs. Interference with incentives to develop innovative devices undermines the public health, and is inconsistent with the purpose of the database to inform patients and physicians of clinical trials for new, innovative treatments and diagnostic products. In other words, the fewer the incentives for investment in innovation, the fewer innovative products will be available to patients and their physicians.

For these and other reasons, and consistent with the Freedom of Information Act, the FD&C Act and the FDA's regulations thoroughly protect study protocols and results information for applicable trials of unapproved or uncleared devices submitted to the agency from the outset of product development. Where the existence of an investigational device exemption (IDE) has not been "publicly disclosed or acknowledged" all data or information in the IDE file is protected from disclosure with two very narrow exceptions. *See* 21 CFR 812.38(b)(3) stating "no data or information in the [IDE] file are available for public disclosure except [data or information related to banned devices, *see* 812.38(b)(1), or adverse events relating to a test subject who suffered from such an event]." Indeed, the fact of the existence of an IDE is confidential and may not be publicly disclosed by FDA as long as a product sponsor does not publicly disclose or acknowledge its existence. 21 CFR 812.38(a). This protection continues until "FDA approves an application for premarket approval of the device subject to the IDE;" [21 CFR 812.38(a)] or finds an IDE substantially equivalent to a predicate device [see 21 CFR 807.95(c)(2)].

The protections for PMA device data or information before approval or denial are as strong as those in the IDE context, if there has been no public disclosure or acknowledgement of the PMA's existence. 21 CFR 814.9(b) & (c). After approval or denial, "any protocol for a test or study" [21 CFR 814.9(f)(2)] or "assay method or other analytical method" is protected from disclosure if the study protocol or test method is "trade secret or confidential commercial or financial information under [21 CFR] 20.61." *See* 21 CFR 814.809(f)(2) and 814.9(f)(5). In other words, FDA's regulations prohibit the scope of release of protocols suggested by the proposed regulation. The scope of protection applies to approved and unapproved devices. Indeed, the FDA's confidentiality regulation in Part 814 specifically protects data or information in the file of unapproved devices when such information is trade secret or confidential

commercial or financial information. In some instances, all data or information in an inactive PMA file is protected from disclosure. Specifically, the regulation states:

(g) All safety and effectiveness data and other information not previously disclosed to the public are available for public disclosure if any one of the following events occurs and *the data do not constitute trade secret or confidential commercial or financial information under [21 CFR] 20.61.*

(1) The PMA has been abandoned. FDA will consider a PMA abandoned if:

(i)(A) The applicant fails to respond to a request for additional information within 180 days after the date FDA issues the request, or

(B) Other circumstances indicate that further work is not being undertaken with respect to it, *and*

(ii) The *applicant fails to communicate with FDA within 7 days after the date on which FDA notifies the applicant that the PMA appears to have been abandoned.*

(2) An order denying approval of the PMA has issued, and all legal appeals have been exhausted.

(3) An order withdrawing approval of the PMA has issued, and all legal appeals have been exhausted.

21 CFR 814.809(f)(2) & (3) (emphasis added).

Simply put, in Part 814 the FDA repeatedly limits disclosure consistent with the FD&C Act and Freedom of Information Act. Nothing that is exempt under the Freedom of Information Act, *see* 5 U.S.C. 552(b)(4), and FDA's regulation implementing that statutory provision, *see* 21 CFR 20.61, may be released to the public, even for unapproved devices. Moreover, even when FDA has grounds to believe that a PMA has been abandoned, the FDA may not disclose any data or information in the PMA that has not already been made public, if the applicant communicates with the agency within seven days of notice from the agency the applicant's intent to continue pursuit of approval. This is consistent with maintaining confidentiality of the existence of PMAs under review and reflects the reality that companies, particularly smaller companies, often stop pursuit of approval for any number of reasons, including for example, a shortage of funds.

The foregoing regulatory protections from disclosure directly reflect the FD&C Act. Under section 520(c), "[a]ny information reported to or otherwise obtained by the Secretary or his representative under section 513, 514, 515, 516, 518, 519, or 704 or under subsection (f) or (g) of this section which is exempt from disclosure pursuant to subsection (a) of section 552 of title 5, United States Code, by reason of subsection (b)(4) of such section shall be considered confidential and shall not be disclosed and may not be used by the Secretary as the basis for reclassification . . . establishment or amendment of a performance standard . . ., except (1) in

Division of Dockets Management (HFA-305)

March 20, 2015

Page 269 of 28

accordance with subsection (h),” Section 520(c) prohibits any disclosure of trade secret and confidential commercial or financial information obtained under the device provisions, including of course, devices cleared through the premarket notification and premarket approval processes, and the inspection provision of the FD&C Act and restricts the use of PMA information to the extent specified in section 520(h)(4).

Consistent with section 520(c), disclosure of PMA data or information pertaining to a device approval or denial is limited to a “detailed summary” that by definition would exclude trade secret or confidential commercial or financial information. *See* 520(c) & (h)(1)(A). Even FDA’s use of PMA data or information is significantly constrained under section 520(h)(4) that permits FDA’s use of PMA data six years after approval. *See id.* This use for approving or reclassifying devices, or establishing performance standards, does not permit disclosure of any data or information in the PMA file, except through the detailed summary required by 520(h)(1)(A). Under (h)(4), FDA may never use trade secrets in the PMA file. Additionally, any disclosure by the agency in the context of approving a device, establishing a performance standard or classifying a device is limited to the detailed summary of safety and effectiveness data that accompanies device approvals and denials, and those summaries cannot contain trade secret or confidential or commercial or financial information. *See* 520(c).

In light of the very forceful prohibitions against disclosure in the FD&C Act and the FDA’s implementing regulations, we believe that HHS’s disclosure of trade secret and confidential commercial information would constitute a taking in violation of the Fifth Amendment. *See Ruckelshaus, Administrator, United States Environmental Protection Agency v. Monsanto Co.* 467 U.S. 986, 1003-1004 (1984). Specifically, the Court in *Ruckelshaus* stated that trade secret property, although intangible, is protected by the Taking Clause of the Fifth Amendment, and is compensable when a regulatory action interferes with a “reasonable investment-based expectation,” *see Ruckelshaus v. Monsanto Co.* at 1010 - 1014. In *Ruckelshaus*, the Court found that during the period from 1972 to 1978, when the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) specifically permitted persons submitting applications for registration to protect their trade secret data or information by declaring the information as trade secret, EPA’s use of that trade secret information would be a taking that had to be justly compensated or else it would result in violation of the Fifth Amendment. *See Id.*

Under the FD&C Act, a regulated person’s claim of a reasonable investment-based expectation exceeds that of regulated persons under FIFRA. There, disclosure and EPA use of trade secret data or information were protected, unless a subsequent applicant provided fair compensation to the person whose property would be affected. The Court fully understood that “[o]nce the data that constitute trade secret are disclosed to others, or others are allowed to use those data, the holder of the trade secret has lost his property interest in the data. *Ruckelshaus v. Monsanto Co.*, at 1011.

As we state above, here under the FD&C Act, disclosure of trade secret data or information is absolutely prohibited whether the data are received in the context of a premarket notification submission or a premarket approval application. Under these circumstances, the proposed rule should not and cannot undermine statutory, regulatory and Constitutional protections, and we

respectfully request that the final rule exclude the trade secret information that is prepared and intended for submission to FDA that the law legally protects from disclosure.

Accordingly, to the extent a protocol is trade secret or confidential commercial information, we strongly recommend that only information about the protocol that will not destroy its confidential character be disclosed in the ClinicalTrials.gov database. The proposed rule should parallel FDA's device law and regulations to avoid undermining Congressional choices, and ultimately, the public health. This can be accomplished by not requiring the disclosure of information that would compromise the confidentiality of clinical protocols.

For applicable trials of cleared or approved devices, we believe relevant clinical trial information is currently captured in the full listing of ClinicalTrials.gov's protocol registration data elements and basic results reporting requirements; the current listing of these data elements provides extensive information on clinical trials and enables interested parties to appropriately evaluate each reported trial.

Disclosure of a full clinical protocol, or information that compromises the confidential character of a protocol such as disclosure of clinical trial information for applicable device trials of unapproved or uncleared devices, will reveal confidential proprietary information about new devices, including their development, *e.g.*, early pilot or feasibility testing, pre-clinical and clinical data development information, and materials, design and construction of the device. Moreover, such disclosure would reveal the culmination of the intellectual process that determined how to study the safety and effectiveness of a device, information which is of considerable value to competitors and, thus, protected confidential commercial information. Disclosure of this information would be very damaging to small company innovators, an economically fragile group, yet enormous contributors to the public health. In effect, receipt of disclosed information like the confidential clinical protocol could have the unintended consequence of eliminating many small device companies from the marketplace and could have a negative long-term impact on patient access to innovative technologies.

The current structure of ClinicalTrials.gov presents understandable information that is consistently formatted for comparison purposes and does not reveal confidential or proprietary information of device sponsors. Additionally, the FDA's laws and regulations controlling disclosure of device information obtained by the FDA under the FD&C Act prohibit disclosure of trade secret and confidential commercial or financial information; additionally, for unapproved devices the existence of IDEs and PMAs, if not publicly disclosed by their device sponsors, may not be disclosed by FDA. Likewise, to the extent IDEs and premarket notifications are not made public by device sponsors, their existence is protected until after FDA issues a substantial equivalence order. Moreover, these regulatory prohibitions against disclosing trade secret and confidential commercial information create a reasonable investment-based expectation of protection from disclosure. As a result, if the government discloses such information, it must justly compensate the affected person, or the disclosure of the information would be an unconstitutional taking under the Fifth Amendment.

Accordingly, we recommend that any requirement to disclose full clinical protocols, or summaries that are tantamount to such a disclosure, or disclosure of clinical trial information for

applicable device trials of unapproved, unlicensed or uncleared devices, be removed from the final rule. Maintenance of the confidential character of protocols developed to demonstrate device safety and effectiveness is critical to encouraging device development and we believe that any advantage from disclosing confidential protocols would be significantly outweighed by the loss of investment in smaller companies, who are often the leading innovators in the device industry.

Completion date – Proposed §11.44(a)(1) provides that clinical trial results must be submitted no later than 1 year after the completion date of the clinical trial, unless a certification for delay is submitted or a request for extension is granted. In accordance with the statutory definition in section 402(j)(1)(A)(v) of the PHS Act, the term “[c]ompletion date” is defined in proposed §11.10 – for a clinical trial – to mean “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. Pages 67, 145, 146, 383 and elsewhere, and related proposed rule provisions.

Comment

AdvaMed recommends expanding the one-year period for submission of basic results information to 18 months as allowed by 402(j)(3)(D)(iv)(I). Doing so would more closely align with global clinical trial reporting requirements which define completion date as last patient, last visit for all protocol endpoints. It would also allow sponsors greater ability to collect and analyze study data according to the plan specified in the protocol rather than artificial deadlines imposed by NIH.

Whereas a 12-month deadline may make sense for “serious and life-threatening disease” drug trials in which regulatory submissions are made based on primary efficacy, it does not make sense for the numerous other types of trials registered in ClinicalTrials.gov that are not designed for an analysis of incomplete information that would effectively constitute an interim analysis. Device trials often collect secondary outcome data collection well past the primary completion date (e.g., mobility functional score at 12 months with the primary outcome measured at 3 months). For these and other trials, an interim analysis with the associated activities (i.e., monitoring visits, data query resolution, table generation, output validation, incomplete safety reporting) represents an inappropriate intrusion by NIH into the design of the protocol and the conduct of the study. Furthermore, the requirement to provide interim results has direct consequences for human subjects by requiring sponsors to enroll more subjects than needed to conduct the trial in order to power the analysis and accommodate the interim database lock.

Extending the deadline for submission of basic results information from 12 to 18 months would allow more sponsors to collect and analyze study data in full prior to the reporting deadline, or to complete the critical processes associated with the interim database lock. This extension would also reduce the burden for both companies and NIH associated with requests for “good cause” extensions to complete data analysis.

In short, requiring a de facto interim analysis specifically to submit data to ClinicalTrials.gov can have the unfortunate and unintended consequence of requiring sponsors of clinical trials to enroll more human subjects than absolutely needed for the trial. For these reasons, NIH should extend the one-year period for submission of results information to 18 months as allowed by the statute.

Adverse Event Reporting – Our proposed definition of adverse event derives from the OHRP definition. We propose to define an adverse event as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.” We do not intend for our proposal to cause an investigator to collect adverse event information of a type or in a way that is not specified in the protocol. We propose to maintain the requirement under the statutory default provisions in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act to submit two tables of information summarizing anticipated and unanticipated adverse events that were collected in accordance with the protocol, i.e., one table for all serious adverse events and one table for other adverse events that exceed a frequency of 5 percent within any arm of the trial. Consistent with the statutory default provisions, our proposal would require submission of information on all such adverse events, not only those that are unanticipated or considered attributable to interventions studied in the clinical trial, to the extent that the collection of these data was specified in the protocol for the trial. We also propose to require responsible parties to submit the total number of participants affected by an adverse event at the organ system level. This information would be required for each arm of the clinical trial and for each adverse event table (serious adverse events and other adverse events). For each organ system class that has one or more adverse events listed in either table, the overall number of participants affected, by arm or comparison group, by any adverse event in that organ system class (see proposed §11.48(a)(4)(ii)(D)), and (4) for each organ system class that has one or more adverse events listed in either table, the number of participants at risk, by arm or comparison group, for any adverse event in that organ system class. Pages 88, 89, 92, 126, 290 and elsewhere, and related proposed rule provisions.

Comment

Section 402(j)(3)(I)(i) and (ii) of the PHS Act required NIH to issue a regulation not later than 18 months after enactment of FDAAA on the best method for including serious adverse events in the database and if NIH failed to do so within 24 months, Congress specified default reporting requirements for serious and frequent adverse events reporting. 402(j)(3)(I)(iii) does not specify reporting total number of participants affected by any adverse event within each organ system for which adverse event data were collected. As a result, NIH does not have authority to require this proposed report and must use the statutory default reporting requirement.

In AdvaMed's June 22, 2009 comments to NIH (see attached), we recommended many improvements to the ClinicalTrials.gov Adverse Event (AE) reporting requirements including that AE reporting for devices be consistent with the definition of serious adverse event used by

the international standard for clinical investigations of medical devices in human subjects (ISO 14155).

NIH failed to issue regulations on AE reporting by the 18- to 24-month deadline required in the statute. This regulation is attempting to create law where there is no longer a legal basis to do so. Further, if this proposed regulatory change becomes final, it will have a negative impact on medical device trials. NIH's proposal to require reporting of the total number of participants affected by any adverse event within each organ system for which adverse event data were collected is a non-standard data element that would not be specified in the protocol and that sponsors would have to generate solely for ClinicalTrials.gov purposes which would be burdensome for device companies. In contrast to drugs which are chemical entities that are metabolized and often have systemic effects (and where it might make sense to report by organ systems), many devices are designed to replace or augment a function of the body and typically act locally, providing readily identifiable physical effects. Due to their local effect, device protocols typically require AE reporting only on organ systems that might be impacted by the experimental device.

What are the requirements for the submission of truthful information? – §11.6 – Section 402(j)(5)(D) of the PHS Act specifies that “clinical trial information submitted by a responsible party under this subsection shall not be false or misleading in any particular.” Pages 119, 330 and elsewhere, and related proposed rule provisions.

Comment

We do not believe a new attestation requirement is needed because ClinicalTrials.gov already requires verification of the record when data is submitted.

In the context of whether clinical trial data or information are false or misleading, NIH should also clarify in guidance that it will consider “intent” including whether the:

- responsible party promptly corrects the noncompliance when provided notice;
- responsible party has engaged in a pattern or practice of noncompliance; or the noncompliance involved may have significantly misled health care providers or patients concerning the safety and effectiveness of the device involved.

NIH should clarify that inadvertent omission of information pertaining to “Other Intervention Names” and “Secondary IDs” would not be considered falsification of data.

FDAAA placed new strict liability prohibited acts that relate to conduct under the registry and results data bank requirements in Section 301 of the FD&C Act. This could subject device companies to significant penalties for minor omissions or inadvertent errors in data entry.

Strict liability is a very unforgiving standard that we do not believe was intended to apply to the highly complex and voluminous data entry that the proposed regulation requires. In light of the significant number of deadlines for data submissions required by the proposed regulation, under

a strict liability standard, companies and their employees could be subject to the charge of making false or misleading statements for unintentional omissions or errors and be exposed to civil, criminal or administrative liability for small, minor mistakes or failures to meet ClinicalTrials.gov deadlines or for unintentional omissions. This is particularly concerning in the device sector which is populated by a significant number of small or start-up companies that may face significant challenges meeting the requirements of the proposed rule. Again, we recommend that NIH clarify in guidance that they will consider intent when determining whether clinical trial data or information is false or misleading.

Principal Investigator (PI) is a term used in the definition of responsible party in section 402(j)(1)(A)(ix) of the PHS Act. For purposes of this proposed rule, principal investigator means “the individual who is responsible for the scientific and technical direction of the study.” . . . We would expect a principal investigator to have full responsibility for the treatment and evaluation of human subjects in the study and for the integrity of the research data for the full study. In keeping with this approach, an investigator for an individual site in a multi-site clinical trial would not be considered the PI unless he or she also has overall responsibility for the clinical trial at all sites at which it is being conducted. Page 144 and elsewhere, and related proposed rule provisions.

Comment

NIH should add a qualifier to designate the PI of the overall trial (e.g., Overall Study PI) and the PI at the individual site. The term PI is typically used both to describe the investigator who has responsibility for a multi-site trial and to refer to the investigator at the individual site. The proposed definition of PI will cause confusion and will result in inaccurate entries.

Combination Products – . . . any applicable clinical trial that studies a combination product would be treated as an applicable drug clinical trial under this proposed rule. Page 169 and elsewhere, and related proposed rule provisions.

Comment

NIH should follow FDA’s determination of the primary mode of action for combination products. Thus, if FDA determines a combination product has a device primary mode of action, the combination product is subject to FDA’s device regulations, and it should be considered a device for ClinicalTrials.gov purposes. The proposal to treat all applicable trials for combination products as drug trials is arbitrary and is inconsistent with the FD&C Act and ignores Congressional intent on the determination of the regulatory pathway of combination products.

In addition, for laypersons, health care providers and researchers who may be interested in more detailed information on the product and may be relying on FDA’s summaries of safety and effectiveness or 510(k) summaries, it will be confusing to see such products categorized as drugs by one government website and as devices on another.

It should be noted that NIH's extraordinary interpretation to treat all combination products as applicable drug trials under the proposed rule denies the PHS Act's statutory protection of delayed disclosure to combination products whose primary mode of action is device-related.

Interventional Study Model characterizes the approach used for assigning groups of human subjects to interventions during the clinical trial. In proposed §11.10(b)(5)(i), the data item is defined as “[t]he strategy for assigning interventions to human subjects.” In ClinicalTrials.gov, responsible parties would be required to select an entry from the following limited set of proposed options: “single group” (i.e., clinical trials with a single arm), “parallel” (i.e., participants are assigned to one of two or more groups in parallel for the duration of the study), “cross-over” (i.e., participants receive one of two alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study), or “factorial” (i.e., two or more interventions, each alone and in combination, are evaluated in parallel against a control group). No “other” option is proposed. Page 178 and elsewhere, and related proposed rule provisions.

Comment

NIH should create an “other” category with a free text box to allow adequate description of alternative study designs. Although NIH provides a number of choices for study design, an “other” category would recognize other possible study designs and allow adequate description of such study designs. This is especially needed for device trials given the diversity of study designs used to evaluate the safety and effectiveness of devices. As the science around design of clinical trial protocols advances, FDA is also accepting newer trial designs (i.e., adaptive trial designs) and allowing for more flexibility including multiple phase designs that transition from three to two arms, for example. Two other scenarios that would fit better under an “other” category than within the short list provided include enrichment designs that employ multiple randomizations during the trial (neither “parallel” nor “cross-over” would adequately describe all variants of this approach), and designs using adaptive borrowing of historical data that permit the case of a single arm of data collected prospectively yet base the analysis on comparisons between purely historical data and a mix of prospective and historical data. This second scenario would be poorly described by either “single group” (which ignores the historical data used in the analysis) or by “parallel” (which improperly addresses the fact that new data is only being collected from a single arm). Modern trial designs such as these are frequently intended to reduce the number of human subjects needed to demonstrate safety and effectiveness. ClinicalTrials.gov should reflect and encourage this trend. As a side note, it would be straightforward to create new categories over time by tracking the examples used in the “other” category. If the “other” category were not used, then the meaning of the existing categories could actually evolve over time with the changing prevalence of different designs that were forced into inappropriate categories.

Intervention Description – The term “intervention description” is not used in section 402(j) of the PHS Act, but we propose it as an additional data element to be submitted as clinical trial information at the time of registration. Based on prior experience, we recognize that

the Intervention Name(s) and Other Intervention Name(s) data elements, whether providing information on brand or non-proprietary names, do not always provide enough information to allow potential human subjects or other users to differentiate among similar interventions used in different arms of a clinical trial, or to distinguish the intervention used in one clinical trial from a similar intervention used in another clinical trial, or to understand the differences between interventions studied in a clinical trial and those used in routine medical practice..... To reduce this ambiguity, additional descriptive information is needed about the intervention, such as information about the dosage, dosage form, frequency of administration, route of administration, and/or duration of administration of a drug, or a general description of the device, including how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as its key components and general types of materials used..... If an experimental device uses different material than previous versions of the device, or than other marketed devices, the responsible party could provide a general description of the new material without including its specific formulation. Page 190 and elsewhere, and related proposed rule provisions.

Comment

As currently described, this field may require device companies to disclose confidential, proprietary business information. As a result, this field should remain optional and should be generic in nature (e.g., “new material” as opposed to a “general description of the new material”).

As described, the intervention description is too detailed and may require sponsors to disclose confidential proprietary information about devices. Requiring companies to disclose proprietary, confidential business information such as how the device functions, its scientific concepts, physical and performance characteristics of the device, and its key components and materials. will inevitably chill and slow innovation on new products for patients as device companies may conduct studies outside the U.S. or reduce the number of trials they conduct in the U.S. in order to protect this important information as long as possible. Disclosure of this information is also likely to disadvantage small device companies who typically account for the vast majority of device innovations and contribute greatly to health care price competitiveness across the industry.

The field should remain optional and should focus on generic descriptions that will not result in disclosure of proprietary information. Moreover, the need for intervention description information may duplicate the description of the study arm that generically describes the study device. To the extent an adequate generic description of the intervention is included in the arm description, there is no need to duplicate that information. To the extent the information is not present in that description, it can be added to this new element in the proposed rule. No matter where it appears, it should not compromise trade secret or confidential proprietary commercial information.

Determination of applicable clinical trial and U.S. FDA Approval, Licensure, or Clearance Status [and delayed disclosure provision for devices] – We propose U.S. FDA Approval, Licensure, or Clearance Status to be submitted as clinical trial information to indicate whether any intervention regulated by FDA and studied in the clinical trial has been approved, licensed, or cleared for any use. Such information would help in ensuring that the data bank operates in compliance with statutory requirements. For example, knowledge of the approval or clearance status of a device is necessary to determine when clinical trial registration information submitted for an applicable device clinical trial may be posted publicly in the data bank. (See section 402(j)(2)(D)(ii) of the PHS Act.) This information also would be helpful for users of ClinicalTrials.gov, including potential participants, who might wish to know whether or not the product(s) under study have been approved, licensed, or cleared for the use studied in the clinical trial. Requiring submission of the approval, licensure, or clearance status for each drug or device studied in an applicable clinical trial would therefore improve and not reduce the clinical trial information available in the data bank, consistent with section 402(j)(2)(A)(iii) of the PHS Act for proposed modifications to clinical trial registration information. Pages 43, 166, 167, 197 and elsewhere, and related proposed rule provisions.

Comment

To determine an applicable device clinical trial, it appears that NIH proposes to utilize a series of questions, in effect an algorithm, which is not described. We would note that applicable device trials are entitled to delayed disclosure under 402(j)(2)(D)(ii). We further understand NIH proposes to eliminate the check box that is currently used by sponsors to denote delayed disclosure of trial information associated with device trials (see footnote on Table 1 of NIH document titled “What Changes from Current Practice Are Proposed in the NPRM?”) and that NIH believes the statute prohibits sponsors who so desire to voluntarily disclose the existence of their clinical trial prior to clearance or approval (p. 43). AdvaMed’s June 22, 2009 comments to NIH (see attached) provided a legal analysis which stated that companies could voluntarily waive the statutory requirement to delay posting of a trial until after FDA clearance or approval. The check box option accomplished this objective and has worked well. We object to NIH’s proposed removal of the check box. If NIH proceeds with an algorithm to determine an applicable device trial, it should be Beta tested with the device industry to ensure that no trial information is released in violation of 402(j)(2)(D)(ii)(I) and (II) which provides for delayed disclosure of clinical trials.

We would also note that NIH’s interpretation that the statute prohibits responsible device parties who so desire, to voluntarily disclose the existence of the trial via the delayed disclosure checkbox, conflicts with congressional intent to encourage voluntary registration of clinical trials [402(j)(4)(A)].

Enrollment Section – 402(j)(2)(A)(ii)(I)(kk) of the PHS Act expressly requires submission of “the target number of subjects” to be enrolled in an applicable clinical trial, but this phrase is not defined. We believe this data element is intended to describe the intended or estimated size of the clinical trial, in terms of the estimated total number of human subjects

(including healthy volunteers) or target number of human subjects who will be enrolled in the clinical trial. We therefore propose in §11.28(a)(1)(xviii) to require the submission of enrollment information at the time of registration, which is described in proposed §11.10(b)(18) as “the estimated total number of human subjects to be enrolled or target number of human subjects in the clinical trial.” We expect that the estimated or target enrollment in a clinical trial might change either before or during the clinical trial, e.g., as recruitment continues. Consistent with section 402(j)(4)(C) of the PHS Act and proposed §11.64(a)(1), a responsible party would be required to update the Enrollment data element not less than once every 12 months, if the anticipated or target enrollment in the clinical trial changes. This update would be in addition to the requirement in proposed §11.64(b) that a responsible party submit the Actual Enrollment data element when recruitment for a clinical trial has ended, i.e., when the Overall Recruitment Status of the trial is changed to “active, no longer recruiting” or “terminated.” This latter requirement is intended to provide users of ClinicalTrials.gov with additional information about the total number of participants enrolled in the clinical trial, which may differ from the target enrollment. (See proposed §11.64(b) and the discussion below of “Overall Recruitment Status” for a discussion of this requirement.) Our proposal for Enrollment is similar to procedures in place for ClinicalTrials.gov prior to FDAAA. Overall Recruitment Status. We propose that the Overall Recruitment Status data element be updated not later than 30 days after a change in the overall recruitment status of the clinical trial. This proposal is consistent with section 402(j)(4)(C)(i)(III) of the PHS Act. We believe that changes in recruitment status should be communicated promptly so that potential human subjects can know whether or not a clinical trial is currently recruiting subjects. Pages 203, 214, 323, 324 343, 443, 444 and elsewhere, and related proposed rule provisions.

Comment

NIH links changes to overall recruitment status to required updates to the actual enrollment data element and apparently will require an update of actual enrollment 30 days after recruiting ends which will be highly problematic. Previously, actual enrollment was updated 30 days after overall study completion. The proposed definition requires the sponsor to account for all screening failures by the time recruiting ends in order to provide an accurate enrollment number. Upon providing “actual” enrollment data to ClinicalTrials.gov, you may find that more patients are needed (e.g., five patients failed to come back for follow-up visits and thus recruitment must begin again to find five additional patients). Depending on how the trial data are collected and verified for any given study, the actual enrollment number may not be available until after study close out monitoring visits are conducted and the study database is locked. Locking the database will be well after the proposed requirement to provide the information “when recruitment has ended,” making it impossible to correct certifications and certify the truthfulness of information any sooner.

It should be noted that the definition of *enrolled* in ClinicalTrials.gov will be inconsistent with many device studies as they are presented in the Summary of Safety and Effectiveness or the 510(k) Summary, which is publicly available on FDA’s website and to which ClinicalTrials.gov is required to link. It is common for device trials to include screening failure in the trial design and for the patients that are enrolled in the study to be those that have passed screening. All

patients would be accounted for in the participant flow module of ClinicalTrials.gov. Allowing this inconsistency will lead to confusion, especially for the lay person.

In general, the PHS Act requires reporting after overall study completion rather than prior to study completion. Additions of more and shorter reporting timeframes add complexity and confusion to the reporting requirements. In general, we believe the proposed rule should define *enrolled* such that it takes into consideration how most device trials are designed. Moreover, NIH should look for ways to streamline and add consistency to reporting requirements and timeframes for required clinical trials which will also encourage more voluntary reporting of clinical trials.

Eligibility Criteria – . . . Clinical trial protocols typically contain lengthy, detailed descriptions of inclusion and exclusion requirements for participants, including, for example, specific laboratory test result values. The requirements are often complex and must be assessed by a clinician or researcher involved in the clinical trial. We believe the submission of all eligibility criteria would be burdensome for responsible parties and, instead of helping prospective participants, would instead prove confusing or overwhelming. Therefore, in proposed §11.10(b)(21), Eligibility Criteria is described as “a limited list of criteria for selection of human subjects to participate in the clinical trial, provided in terms of inclusion and exclusion criteria and suitable for assisting potential human subjects in identifying clinical trials of interest.” Page 205 and elsewhere, and related proposed rule provisions.

Comment

We concur that listing all eligibility criteria would be burdensome for responsible parties and confusing for participants. We recommend that NIH add a statement that not all the inclusion/exclusion criteria will be listed in ClinicalTrials.gov so that participants understand that they may meet all the listed eligibility criteria but may not ultimately be eligible for the trial because of an enrollment criterion in the protocol that was not listed in ClinicalTrials.gov. The statement should also remind potential participants that they can reach out to the trial facility contacts for complete inclusion/exclusion criteria.

The Agency believes that for applicable device clinical trials of devices that previously were approved or cleared it is permissible and appropriate to post registration information prior to the deadline. Posting this information prior to the deadline would be consistent with the objectives of expanding the registry and results data bank by rulemaking, facilitating enrollment in clinical trials and providing a mechanism to track subsequent progress of clinical trials. (See sections 402(j)(2)(A)(i) and (3)(D)(i) of the PHS Act.) Conversely, waiting to post registration information for applicable device clinical trials of devices that previously were approved or cleared until after results information is required to be posted would delay access to information about such clinical trials and would eliminate the possibility for the data bank to be used to facilitate enrollment in such trials and to allow the public to track such trials while they are ongoing. The Agency proposes in §11.35(b)(1)

to post registration information for an applicable device clinical trial of a device that previously was approved or cleared “not later than 30 calendar days after clinical trial results information is required to be posted in accordance with §11.52 of this part.” However, in light of the objectives of the data bank discussed above we intend, in practice, to post registration information for such applicable device clinical trials as soon as practicable after submission, but not later than 30 calendar days after clinical trial results information is required to be posted. Page 245 and elsewhere, and related proposed rule provisions.

Comment

The proposal to post registration information as soon as practicable after submission but not later than 30 calendar days after trial results are required to be posted fails to distinguish between a new trial for the same product that has been cleared or approved with the same indication/use and a trial for a product that has been cleared or approved for a new un-cleared or unapproved indication/use. As a result, the proposal is in direct contravention of the statute [402(j)(2)(D)(ii)(I) of the PHS Act] which provides for delayed disclosure of device clinical trials for a device that was not previously cleared or approved. To comply with the statute, NIH must provide for delayed disclosure for trials for cleared or approved products for new un-cleared or unapproved indications/uses.

The statute is very clear that trials for products that have not been previously cleared or approved (i.e., new products or new indications for existing products) are subject to the delayed disclosure provision. As a result, NIH should make this distinction in the rule.

Applicable device clinical trials of devices that have not been approved or cleared previously – Section 402(j)(2)(D)(ii)(I) of the PHS Act provides that for applicable device clinical trials of devices that have not previously been approved or cleared (i.e., unapproved or un-cleared devices), registration information must be posted publicly not earlier than the date of approval or clearance of the device and not later than 30 days after such date. Proposed §11.35(b)(2) reflects this statutory provision. In order to help us meet the posting deadline and identify the set of applicable device trials for which registration information needs to be posted after approval or clearance of a device, we have included a requirement in proposed §11.64(b)(2) for the responsible party to update the U.S. FDA Approval, Licensure, or Clearance Status data element not later than 15 calendar days after a change in status has occurred. The responsible party would be required to update that data element for all applicable clinical trials that study the device that was approved or cleared. Pages 245 – 246 and elsewhere, and related proposed rule provisions.

Comment

As stated above, to comply with the statute, the rule needs to distinguish between a new trial(s) for the same product that has been cleared or approved with the same indication/use and a trial(s) for a product that has been cleared or approved for a new un-cleared or unapproved indication/use. Further, in general, the statute makes clear that updates to ClinicalTrials.gov by the responsible party are on an annual (12-month) or on a 30-day basis, not 15-day increments.

The statute does not specify that reporting requirements by responsible parties must factor in NIH time. As a result, the rule should change the update requirement to 30 days.

Submitting results information following initial product approval, licensure, or clearance – Proposed §11.44(a)(2) would require that results information be submitted by the earlier of 1 year after the completion date, or 30 calendar days after FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial. Page 250 and elsewhere, and related proposed rule provisions.

Comment

The proposed rule is inconsistent with the statute because it leaves out the statutory language of “not later than 1 year.” 402(j)(3)(E)(i) states that results for applicable trials are due not later than 1 year after the earlier of the estimated completion date or the actual completion date except in the case of devices seeking approval of a new use [402(j)(3)(E)(v)] in which case it states that results are due not later than 1 year after the earlier of the date that is 30 days after the new device is cleared or approved, or after the Secretary issues a not substantially equivalent (NSE) or not approvable letter, or the 510(k) or PMA is withdrawn. The proposed rule could result in the perverse situation where a trial that ends 3 months prior to FDA approval or clearance would not have sufficient time (i.e., the statutorily mandated 1 year) to post results after the study completion date.

Delayed results with certification – §11.44(b) and (c). Pages 251 – 255 and elsewhere, and related proposed rule provisions.

Comment

For results submissions associated with applicable trials for devices seeking approval, licensure or clearance of a new use (versus an initial use), the proposed rule appears to indicate it will require results submissions 30 days after FDA issues an NSE or not-approvable letter. The proposed rule appears to assume that responsible parties would not continue with product development, or to assume that the product has been abandoned once FDA sends the NSE or not approvable letter. However, the statute provides companies with up to 210 days to resubmit the application or PMA (see 402(j)(3)(E)(v)(I)(cc)). It is incorrect to assume that the product has been abandoned and the rule should be changed to allow responsible parties to continue with product development without disclosure of trial results even after receiving an NSE or non-approvable letter for products associated with a new use. Trade secret or confidential commercial information could be prematurely disclosed both in trials for devices for new uses and for initial uses and no distinction should be made between the two approaches. Importantly, FDA’s regulations prohibit FDA disclosure of NSE results because an NSE classifies a device into Class III, requiring a PMA. *See* 21CFR 807.95(c)(2).

The proposed rule should also be changed to allow related good cause extensions for delayed disclosure of device trial results for both initial and new uses as well as for products that have received an NSE or non-approvable letter.

“We do not believe that results submission should be delayed for applicable clinical trials of products that the sponsor has no intention of marketing or for which product development has been abandoned.” Page 254 and elsewhere, and related proposed rule provisions.

Comment

The proposed rule fails to account for situations in which product development may be delayed or put on hold due to funding issues or priority setting within a company (e.g., a company pursues other products where the opportunity for FDA clearance or approval is judged to be faster before returning to the product in question). Companies may also decide to pursue the product outside the U.S. before returning to the U.S. market – in which case the product has not been abandoned. The device industry in particular must frequently put device development on hold because funding has run out and a new round of funding must be sought from investors. In each of these scenarios, there is a continued need for protection of companies’ confidential, proprietary business information.

We also take issue with the trigger that NIH proposes to use to determine whether results submissions should be delayed for products which are under development. The proposed trigger appears to be that the responsible party is conducting subsequent clinical trials on the product. The conduct of subsequent clinical trials is not the only marker for determining whether a product remains under development. For example, a company may have determined that certain design changes are appropriate before conducting a subsequent clinical trial. It should be noted that for the vast majority of products, sponsors will have invested millions of dollars in the research and development of the product including non-clinical and clinical trial data. In order to promote continued device innovation in the U.S., the rule should continue to protect companies’ confidential, proprietary business information.

Since NIH cannot intuit a company’s intentions, in order to require submission of results, the rule should create a mechanism by which responsible parties can affirmatively declare that they have abandoned product development and that as a result, trial results will not be posted. The process should also allow companies to indicate that the project was abandoned before results were obtained so no results will be posted.

NIH states “for purposes of proposed 11.44(c), the first 510(k) cleared for a particular device type would be considered ‘initial clearance’ of the device. For example when a device is reclassified from Class III to Class II, then the first 510(k) that is cleared as having demonstrated substantial equivalence to the reclassified device would be considered the initial clearance of the device. Consequently, for purposes of proposed 11.44(b), all other 510(k)s cleared for a device type other than the first one, would be considered clearance of a new use.” Page 260 and elsewhere, and related proposed rule provisions.

Comment

NIH appears to cite the infrequent example of a device being down-classified from Class III to Class II to misinterpret the PHS Act and the FD&C Act. The rule should be consistent with long-held legal interpretations of the FD&C Act. Congress defined an applicable device trial in 402(j) in terms of the FD&C Act (i.e., a prospective study of health outcomes comparing an intervention with a device subject to 510(k), 515 or 520(m)). Although FDA reviews 510(k) submissions under the substantial equivalency review standard, each sponsor's 510(k) is treated independently from a previous sponsor's "predicate" 510(k) as a new 510(k) (i.e., initial use or initial clearance of the new 510(k)). All 510(k)s are considered an initial use or initial clearance, therefore, it is inappropriate to treat all other 510(k)s cleared for a device type as clearance of the same use. Even in the example cited by NIH of a Class III down-classified to Class II, all subsequent 510(k)s by different sponsors would be for an "initial clearance or initial use" not a "new use" as that term is used in the PHS Act. In short, every 510(k) is an initial clearance by operation of the FD&C Act. We would also note that Congress intended delayed disclosure to apply to trials for new uses of an existing device.

It should be noted that it appears NIH's extraordinary interpretation of FFDCFA allows NIH to treat virtually all trials for 510(k) devices as trials for new uses (as opposed to initial uses) under the PHS Act and thus not subject to the statute's delayed disclosure provision, in contravention of this statutory protection for devices.

Two-Year Limitation of Delay – §11.44(b)(2) and (c)(2). Pages 256, 257, 416 and elsewhere, and related proposed rule provisions.**Comment**

There are many legitimate reasons a company may be delayed in pursuing product development including but not limited to loss of funding or reprioritization of projects in order to obtain what may be judged to be a faster FDA clearance or approval on another product (to provide a stream of income for the delayed product). The rule is unclear as to whether good cause extensions can exceed the two-year limitation. NIH should clarify that good cause extensions are in addition to the 2-year limitation.

We invite public comment on these specific situations and on more general criteria that could be used to determine what constitutes good cause for an extension. Pages 264-266 and elsewhere, and related proposed rule provisions.**Comment**

There are many legitimate reasons a company may wish to file for a good cause extension to delay results while pursuing product development. The following are legitimate reasons for good cause extensions and should be included on in the rule:

1. Device trials supporting product deemed not approvable or not substantially equivalent;

2. Device trials stopped for reasons unrelated to safety which remain under product development;
3. Good cause extensions for device trial results for initial 510(k) clearances, again to include each and every 510(k) clearance, and for initial PMA use and for new PMA uses;
4. Trials with a primary completion date in advance of the overall completion date for which an interim analysis is not included in the protocol;
5. Device trials certifying initial approval that, if approval has not been granted at the end of the 2-year period and the responsible party intends to continue with product development, a good cause extension should be granted;
6. Device trials certifying a new use that, if the responsible party has not filed the application within 1 year and still intends to file, a good cause extension should be granted; and
7. Device trials supporting a product that has been stopped but development of the product has not been abandoned.

In these situations, disclosure of information related to the trial may disclose confidential commercial information or technology. There may be other appropriate reasons for good cause extensions that are not listed above. In general, companies should be granted good cause extensions where product development has not been abandoned.

Posting of information about certifications for delayed submission and about good cause extensions. In order to provide responsible parties with insight into the general types of reasons that have and have not been considered to constitute good cause for an extension, we propose to post and update periodically on the ClinicalTrials.gov website a generalized list of reasons for which extensions have and have not been granted. Pages 268 – 271 and elsewhere, and related proposed rule provisions.

Comment

We concur with NIH's analysis that posting information about the reasons used to delay results submission could result in the posting of information that might be considered confidential. However, even the proposed rule's generalized list might disclose confidential information (i.e., “. . . we would *attempt* [emphasis added] to remove from the list any information that might allow a user to identify a specific applicable clinical trial.”). The way NIH proposes to implement this element, it is not clear NIH could remove enough information to prevent a particular reason from being traced back to a particular trial. If NIH wants to create such a generalized list, it should be presented to users of the website as a standardized list of possible reasons trials may be delayed as opposed to a list that could relate to a specific trial or trials.

We invite comments on whether or not we should require the submission of additional demographic or baseline characteristics that were collected during the clinical trial, the advantages and disadvantages of requiring the submission of such information, and, if so, how such information can be specified in the rule. Page 277 and elsewhere, and related proposed rule provisions.

Comment

Submission of additional demographic or baseline characteristics (e.g., country of origin/residence) that were collected during the trial should not be required as these subsets of data may not be statistically significant, and may be misleading and cause confusion. Making public these subsets of data may also be seen as promotional beyond FDA approved labeling.

Although we understand the theoretical benefit that providing additional demographic and baseline data could provide, this benefit must be balanced against the documented burden associated with meeting the requirements of registering trials and posting basic results. The assumption that certain additional baseline and demographic information is typically collected in protocols is not accurate. Requiring sponsors to design studies for the purpose of collecting additional information strictly to fulfill ClinicalTrials.gov reporting purposes stands in stark contrast to NIH's stated general consideration, "It is important to note that this proposed rule does not impose any requirements for the design or implementation of a clinical trial or for the collection of information during a clinical trial" (p. 34).

§11.48(a)(3)(v) – We specify in proposed §11.48(a)(3)(v) the information that a responsible party must submit for any scientifically appropriate analysis: (A) Statistical Analysis Overview: The responsible party would identify the arms or comparison groups compared in the statistical analysis (by selecting the arms or comparison groups already defined for the outcome measures) and specify the type of analysis conducted. The type of analysis conducted would be selected from the following limited set of options: "superiority," "non-inferiority," "equivalence," or "not applicable," where "not applicable" would be appropriate for a single group analysis, for example. No "other" option is proposed. Pages 283, 284, 425 and elsewhere, and related proposed rule provisions.

Comment

NIH identifies a limited set of options that would be available (i.e., superiority, non-inferiority, equivalence, or not applicable). We recommend that the proposed rule be expanded to include two new categories: "Estimation" and "Descriptive." It can be that certain analyses are simply about estimating certain quantities (such as the rate of events in a given arm, rather than a comparison between rates in two arms). Also, many safety analyses in particular are inherently descriptive rather than inferential, and would be better captured with a "descriptive" moniker.

§11.48(a)(3)(v)(A), (B) and (C) – The proposed rule states "Statistical analysis results of scientifically appropriate statistical analyses, if any, include any statistical analysis that is: A) pre-specified in the protocol and/or statistical analysis plan that was performed on the outcome measure data, B) made public by the sponsor or responsible party prior to the date on which results information is submitted for all primary and secondary outcome measures studied in the clinical trial, or C) conducted in response to a request made by the FDA prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial." Pages 282 283, 285, 425 and elsewhere, and related proposed rule provisions.

Comment

§11.48(a)(3)(v)(C) should be revised in the following manner:

(C) Conducted on the primary outcome measure in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial. . . .

We believe the scope of (C) is extremely broad and could be quite burdensome as currently proposed. The requirement to report statistical analyses should be restricted to FDA requests for statistical analyses on primary outcome measures only. It is not unusual for there to be extensive questioning and dialogue between the responsible party and FDA during the course of the trial, during the submission process, or as part of preparation for an FDA Advisory Panel meeting. Such requests can include analyses on different analysis sets, examinations of numerous subgroups, or applications of methods not originally specified in the protocol or analysis plan. These analyses are frequently ad hoc or exploratory in nature and many are not investigated further after initial examination. The fact that many of these findings are not deemed relevant can be inferred from their broad exclusion from the product labeling. An appropriate balance between transparency of information that is accessible to the public and the volume of data that can be requested by FDA would be achieved by restricting the scope of (C) to primary outcome measure analyses only.

Administrative Information – Results point of contact telephone number and email address. §11.48(a)(5). Pages 271, 396, 429 and elsewhere, and related proposed rule provisions.

Comment

§11.48(a)(5) requires the name or official title of the point of contact and the telephone number and email address of the point of contact. This is defined as the name, official title, organizational affiliation, physical address, mailing address, phone number and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

We agree that it is very important to name a contact point, however, naming individuals or employees can be problematic. This information is also held private in other government databases. In lieu of naming an individual, we recommend allowing responsible parties to list a function (e.g., clinicaltrials@companyabc.com) rather than an individual point of contact. There are personal privacy reasons that individuals or designated employees may not want their work address and email listed in a public U.S. government database. In addition, individual points of contact may change frequently, requiring responsible parties to update ClinicalTrials.gov too frequently.

§11.48(b) – Redacted final report required to be submitted. This section requires a redacted final report be submitted to NIH. . . . for each pediatric postmarket surveillance of a device that is not a clinical trial, we believe that the final report *would contain a*

suitable summary of the surveillance results, and we propose that it be submitted to ClinicalTrials.gov in a form that can be made available to the public. Pages 44 – 45 and elsewhere, and related proposed rule provisions.

Comment

This should be revised to allow the manufacturer to alternatively submit a suitable summary of the pediatric postmarket surveillance of the device rather than a full final report that is redacted. NIH itself acknowledges that “pediatric postmarket surveillances under section 522 of the FD&C Act can take various forms [other than a clinical trial], including a detailed review of the complaint history and the scientific literature, non-clinical testing, observational studies” FDA’s Guidance for Industry and FDA Staff entitled *Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act* provides examples of postmarket surveillance which “illustrate a range of surveillance methods” including “telephone or mail follow-up of a defined patient sample,” “non-clinical testing” including “analysis of devices explanted from animal models....”, and “use of secondary data sets (e.g., Medicare), registries (e.g., Society for Interventional Radiology stent registry), internal registries, or tracking systems.” Redacted reports of such postmarket surveillance methods might be confusing and virtually unreadable. We believe a summary of pediatric postmarket surveillance studies that are not clinical trials would be much more useful and helpful to the intended audience of ClinicalTrials.gov than a redacted report.

Definition of “Enroll or enrolled.” Page 384 and elsewhere, and related proposed rule provisions.

Comment

The definition of *enroll* or *enrolled* should be expanded to add “unless specifically defined differently in the protocol.” Not all studies consider the point of enrollment the signing of informed consent. Further, in some limited circumstances, the signing of informed consent is not required.² The preamble of the proposed rule has stated, with respect to other data elements, that

² Part 50, Protection of Human Subjects requires:

Sec. 50.27 Documentation of informed consent.

(a) Except as provided in Sec 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

Part 56, Institutional Review Boards allows:

Sec. 56.109 IRB review of research.

(c) An IRB shall require documentation of informed consent in accordance with Sec. 50.27 of this chapter except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject’s legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, or

(2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.

it is not NIH's intention to require collection of data beyond those required by the protocol. We agree with that and believe it should be applied in this instance as well. While presumably unintentional, this definition appears to place NIH in the position of dictating study design which is within the sponsor and FDA's purview. The current definition may also result in a situation in which enrollment numbers for a specific trial will be different on the ClinicalTrials.gov website than in FDA's 510(k) Summary or Summary of Safety and Effectiveness to the cleared or approved product, respectively, to which ClinicalTrials.gov is required to link. Also see our comments on enrollment on pages 16 – 18 above.

Definition of "Gender." Page 392 and elsewhere, and related proposed rule provisions.

Comment

Replace "gender" with "sex" everywhere that it appears in the proposed rule in order to be consistent with FDA guidance. FDA recently issued guidance entitled *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* which included a discussion of the terms "gender" and "sex" referencing an Institute of Medicine (IoM) study by the Committee on Understanding the Biology of Sex and Gender Differences. Per FDA and IoM, "sex" refers to classification by reproductive organ while "gender" refers to a person's self-representation as male or female based on the individual's gender presentation.

Definition of "Why Study Stopped." Page 393 and elsewhere, and related proposed rule provisions.

Comment

The definition of why the study stopped should be limited to whether the study was stopped for safety reasons, i.e., why study stopped means, for a clinical trial that is suspended or terminated or withdrawn prior to its completion as anticipated by the protocol, a brief explanation of the reason(s) why such clinical trial was stopped, if the study was stopped for safety reasons.

We believe safety reasons (e.g., adverse events, new safety information about a class of therapies) should be noted. However, all other reasons are a subset of 'business reasons' which should not require disclosure to avoid disclosing confidential commercial information about the strategic and financial operations of the company.

Adverse Event Information – Page 426 and elsewhere, and related proposed rule provisions.

Comment

Change: "collected during" to "collected per protocol during."

Division of Dockets Management (HFA-305)

March 20, 2015

Page 289 of 28

As stated in the preamble, it is not the intention of this regulation to require collection of adverse events beyond those required by the protocol. Also see our comments on Adverse Events on pages 11-12 above.

§11.66 Requirements for corrections of clinical trial information. Page 446 and elsewhere, and related proposed rule provisions.

Comment

Companies cannot enter corrected data until it is available. Thus, paragraph (a) should be revised to read:

Correction of errors. A responsible party who becomes aware of errors in any clinical trial information submitted under this part or is informed by NIH that such clinical trial information contains errors shall correct such errors not later than 15 calendar days after the date on which the corrected data becomes available

In closing, thank you for this opportunity to provide comment on NIH's Proposed Rule and Request for Comments on Clinical Trials Registration and Results Submission and the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Please do not hesitate to contact me if you have any questions.

Sincerely,

Tara Federici
Vice President
Technology and Regulatory Affairs



June 22, 2009

Deborah A. Zarin, **M.D.**
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National Library of Medicine
9000 Rockville **Pike**
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Bethesda, **MD** 20894

Docket No. NIH-2009-0002: Notice of Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank; Request for Comments

Dear Dr. Zarin:

On behalf of AdvaMed, the Advanced Medical Technology Association, I am pleased to submit these comments in response to the National Institutes of Health's (**NIH**) request for input on issues the Agency will consider as it develops regulations to expand the clinical trial registry and results data bank (ClinicalTrials.gov) per Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA).

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed's members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the health care technology purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually.

AdvaMed Comments on NIH Topics and Questions

In response to the topics and questions posed in the NIH's March 23, 2009 Federal Register Notice, AdvaMed has prepared the following responses below. AdvaMed also raises a number of important additional areas of concern to device manufacturers associated with the implementation of Section 801 of FDAAA in our response to Question 11.



- 1. Whether to require submission of results information for applicable clinical trials of drugs, biological products, and devices that are not approved under sections 505, 515, or 520(m) of the FDC Act, licensed under section 351 of the PHS Act, or cleared under section 510(k) of the FDC Act (whether or not clearance, approval or licensure was sought). Please comment on issues such as the potential advantages and disadvantages to the public and public health of disclosing results information for trials involving drugs, biological products, and devices that are not approved, licensed, or cleared; the effects (if any) on the development of drugs, biological products, and devices; the reporting burden on data submitters; and the appropriate timing of submission and public disclosure of information, taking into account the certification process established by the FDAAA when approval, licensure, or clearance is sought for a product under study in an applicable clinical trial. In particular, consider scenarios involving trials of different types of unapproved products: (a) Applicable clinical trials of products for which marketing applications or premarket notification submissions are never submitted to the (Food and Drug Administration (FDA); (b) applicable clinical trials of products for which marketing applications or premarket notification submissions are submitted, but a decision is pending; and (c) applicable clinical trials of products for which marketing applications or premarket notification submissions are submitted and the FDA decides not to approve, license, or clear the product for marketing.**

AdvaMed Response

Trials Stopped for Safety Issues

AdvaMed supports results disclosure associated with clinical trials for certain medical devices that are not approved under Section 515, 520(m) or deemed Not Substantially Equivalent (NSE) under 510(k). Specifically, AdvaMed supports results disclosure on ClinicalTrials.gov for both Significant Risk (SR) and Non-Significant Risk (NSR) device trials for PMA or 510(k) products if a trial were stopped prior to approval or clearance for safety issues. Similarly, AdvaMed supports results disclosure for products that are not approved under Sections 515, 520(m) or cleared under Section 510(k) for safety reasons where the sponsor decides to discontinue the approval or clearance process. Disclosure of results for device trials stopped due to a safety issue meets both the spirit and the intent of Section 801 of FDAAA. Disclosure of results in these instances serves the function of informing trial participants and the general public, and importantly, would potentially act to protect future human subjects from participation in trials for similar products that may present analogous risks.

There are other scenarios involving medical devices that are not approved under Sections 515, 520(m) or cleared under Section 510(k) in which AdvaMed does not believe it is appropriate to disclose clinical trial results until after approval or clearance. In a small subset of medical device trials, it may never be appropriate to disclose results.

Trials Deemed Not-Approvable or Not Substantially Equivalent

Specifically, in situations in which a PMA or 510(k) application is submitted to FDA and it is deemed not approvable or not substantially equivalent (NSE) but the company

intends to resubmit the application, then we believe the results should not be required to be submitted until 30 days after the product is approved or cleared. There are important device distinctions that are relevant in this scenario. Many devices are engineered products designed to replace, repair or augment a function of the body. Thus, an engineering or design change may rectify a problem with the device enabling a new and successful FDA application. Additionally, in these instances, we believe a good cause extension should apply. Further, AdvaMed recommends the creation of a text box in ClinicalTrials.gov enabling a company to briefly explain the reasons for the delay in results information. See also the last bullet in our response to Question 9 section “g.”, involving trials where the company intends to resubmit the application.

Trials Stopped for Reasons Unrelated to Safety

Finally, in a small subset of incompleting medical device trials, AdvaMed believes it is inappropriate to disclose results. Medical device trials may be stopped for reasons unrelated to safety but rather due to an inability to obtain continued financing, or due to changed company priorities, as examples. In these circumstances, disclosure of information related to the trial may disclose confidential commercial information or technology in violation of the FDC Act, FDA regulation and Freedom of Information Act bans on disclosing information related to an Investigational Device Exemption (IDE).¹ It may also disclose confidential or proprietary information to a company’s competitors preventing the original company from successfully pursuing the affected technology later. Because the product was never FDA approved or cleared, the device cannot be marketed and thus cannot present risks to patients or the public. In these rare instances, we believe the incomplete trial results should not be released.

In sum, except in the two different situations described above, AdvaMed supports results disclosure on ClinicalTrials.gov for both Significant Risk (SR) and Non-Significant Risk (NSR) device trials for PMA or 510(k) products if the trials were stopped prior to approval or clearance for safety issues.

- 2. Whether narrative summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional. Comment on issues such as the potential advantages and disadvantages to patients, research subjects, and the public of requiring responsible parties to submit narrative summaries that are written in non-technical, understandable language for patients; the utility to the scientific community of requiring responsible parties to submit narrative summaries written in technical language; the content and structure of any such narratives; and procedures that could be established to help ensure the content is not misleading or promotional.**

¹ The protocol is part of the Investigational Device Exemption (IDE) which is protected confidential commercial information under the Freedom of Information Act (5 U.S.C. §552), the FDC Act and FDA regulations (21 C.F.R. Part 20).

AdvaMed Response

AdvaMed's responses to questions 2 and 3 are combined in the response to Question 3.

- 3. What additional information, if any, that is written in non-technical, understandable language for patients should be required to be submitted to the data bank or should be provided in the data bank to assist patients in understanding and interpreting the information available in the data bank. Please consider the types of information that would best assist patients and other members of the public in understanding and interpreting results information in the data bank, including information on adverse events. Comment on issues such as the types of information that might assist patients and the public in understanding the results of individual clinical trials and of clinical trials in general. Identify existing sources of explanatory information that are oriented toward patients and the public and could be included in or linked to the data bank.**

AdvaMed Response to Questions 2 and 3

AdvaMed supports the provision of both technical and non-technical summaries of results for trials associated both with approved or cleared and unapproved or NSE devices (subject to the exceptions noted in our response to Question 1 for trials associated with certain unapproved or NSE devices) in ClinicalTrials.gov.

As a practical matter, many patients will likely read both the technical and the non-technical summary. Thus, to ensure transparency and reduce confusion for patients reading both the technical and non-technical summaries, data elements between the two summaries should be consistent.

AdvaMed supports the use of a structured summary in abstract form for both the technical and non-technical summaries. The sole difference would be the level of language used in the summaries, to ensure that non-technical summaries will be accessible to general users of the database. AdvaMed recommends the summaries should be no more detailed than what one commonly finds in a journal abstract and include a word limit (e.g., 250-300 words as suggested in the CONSORT Statement for reporting randomized trials in journal and conference abstracts²). AdvaMed has recommended a list of data elements or sections of a summary in Table A below. Some of the data elements may be automatically populated by the database (as ClinicalTrials.gov has done for other results data elements) where the information was previously required (e.g., registration data elements). This structured format would ensure consistent presentation of clinical trial information and would facilitate a review or quality check by ClinicalTrials.gov.

² CONSORT for Reporting Randomised Trials in Journal and Conference Abstracts. www.thelancet.com.
Published online January 22, 2008.

Table A: Proposed Data Elements To Be Addressed in Technical and Non-Technical Summaries
Study Title
Study Device/Therapy/and or Components
Study Population
Indication/Intended Use Studied in Trial
Study Design Overview
Study Objective(s)
Primary Endpoint(s)
Secondary Endpoint(s)
Summary of Clinical Study Results including Sample Size
Risks and Benefits (includes Adverse Events)
Warnings/Precautions/Contraindications if applicable <ul style="list-style-type: none"> • Please list any warnings, precautions or contraindications for previously cleared or approved device
Approval or Clearance Status Please list any indications previously cleared or approved for this device

As discussed above, the requirement to provide technical and non-technical results summaries for unapproved or NSE products would apply only to those clinical trials that were not completed due to safety reasons or to those products that are not approved or cleared under Section 515, 520(m) or 510(k) for safety reasons where the sponsor decides to discontinue the approval or clearance process.

If the trial were stopped for reasons other than a safety issue (e.g., lack of funding), the summaries would not be required. For example, medical device trials may be stopped for reasons unrelated to safety such as changed company priorities. In these circumstances, disclosure of information related to the trial may disclose confidential or proprietary information or technology in violation of the FDC Act and other bans on disclosing information related to an Investigational Device Exemption (IDE). Because the product was never FDA approved or cleared, the device cannot be marketed, and thus, cannot present risks to patients or the public. In these rare instances, the requirement to provide technical and non-technical summaries would not apply.

In situations where products are not approved under Section 515, 520(m) or are deemed NSE under 510(k) and the sponsor intends to continue the approval or clearance process,

the sponsor should be given an opportunity to seek a good cause extension, thus enabling technical and non-technical summaries to be submitted after approval or clearance. The requirement to provide the summaries would apply to unapproved or NSE products where the applicant is continuing to seek approval or clearance only *after* the product is cleared or approved.

AdvaMed is however, concerned about the possibility that posted summaries of results may jeopardize the ability to publish the clinical study results in the scientific literature if the International Committee of Medical Journal Editors (ICMJE) or other journal editors view such summaries as prior publication. The ICMJE updated their Uniform Requirements for Manuscripts Submitted to Biomedical Journals in October 2008 indicating: “The ICMJE does not consider results posted in clinical trial registries as previous publication if the results are presented in the same, ICMJE-accepted registry in which initial registration of trial methods occurred and if the results are posted in the form of a brief structured abstract or table.” Additionally, the ICMJE posted an FAQ document on Clinical Trials Registration in October 2008 reporting: “. . . thus the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, . . . [ICMJE] may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication.” (See www.ICMJE.org). AdvaMed encourages the National Library of Medicine (NLM) and FDA to work closely with ICMJE to ensure that the inclusion of technical and non-technical summaries of results information in the data bank is not considered prior publication.

We understand that some organizations have indicated they support the use of the ICH E3 Annex 1 Synopsis as a format for trial result summaries. ICH E3 is tailored for drug trials. If a structured format tailored to devices is technically unachievable, AdvaMed could support the use of the ICH E3 format if modifications were made to it to reflect data elements that are relevant to device trials.

The following are specific topic headings in the ICH E3 Synopsis format with proposals for modified headings to ensure applicability to device clinical trials. We propose expansion of the headings versus replacement considering the increase in combination therapy trials (e.g., drug and device combination product).

- “Name of Active Ingredient” – with respect to devices, add Note: N/A or not applicable for device clinical studies.
- “Phase of development” – with respect to devices add Note: N/A or not applicable for device clinical studies.
- “Test product, dose and mode of administration, batch number” – with respect to devices add “Test product, therapy, device, or components (for combination drug/device products include dose, mode of administration and batch number for drugs)”

- “Reference therapy, dose and mode of administration, batch number” – with respect to devices add “Reference product, therapy, device, or components (for combination drug/device products include dose, mode of administration and batch number for drugs)”

Since the ICH E3 Synopsis format can be up to three pages long, it will also be important to ensure that use of this format does not jeopardize publication in the scientific literature.

See our response to Question 6 below for recommendations on the timeline for technical and non-technical summaries.

- 4. Whether to require submission of the full clinical trial protocol or only such information on the protocol as may be necessary to help evaluate the results of the trial. Comment on the value of the full clinical trial protocol versus partial information from the protocol in evaluating the results of a trial and the completeness of results data submission.**

AdvaMed Response

AdvaMed supports providing complete information on clinical trials for approved and unapproved products (subject to the exceptions identified in our response to Question 1). We believe full and complete clinical trial information is currently captured in the full listing of ClinicalTrials.gov’s protocol registration data elements (as reflected in the August 20, 2008 Draft Protocol Data Elements Definitions document) and in basic results data elements (as reflected in the March 9, 2009 Draft “Basic Results” Data Element Definitions document). By “full listing,” AdvaMed means all data elements in both documents including those identified as required or conditionally required by ClinicalTrials.gov and required/may be required to comply with Section 801 of FDAAA. We believe the full listing of protocol registration and basic results data elements provides extensive information on a clinical trial and enables interested parties to appropriately analyze a trial. Please note that we are recommending that one additional data element be added to the Adverse Events (AE) data elements (see the AdvaMed Response to Question 9 below).

AdvaMed does not support providing the *full protocol* for approved and unapproved products for a number of reasons. Disclosure of the full protocol would violate existing FDC Act and other requirements. The protocol is part of the Investigational Device Exemption (IDE) which is protected confidential information under the FDC Act and Freedom of Information Act. In the device arena, disclosure of the full protocol will reveal proprietary and confidential information about the actual device including device development (e.g., early pilot or feasibility tests, and pre-clinical and clinical data development background), materials, design, and construction of the device. This information will not be useful or helpful to the vast majority of patients but it will expose confidential and proprietary information to competitors.

Small companies account for a vast number of device innovations and contribute greatly to maintaining strong price competitiveness across the industry (nearly 70 percent of AdvaMed's members are small companies). In many instances, small companies are willing to invest in developing technologies for niche and orphan markets – patient communities that may otherwise be overlooked and underserved.

Disclosure of the full protocol would essentially provide a roadmap (both on the design of the trial and on the actual device) for competitors to follow and could provide significant advantages to competitors who could speed a competing device into clinical trials and obtain FDA approval or clearance in order to take advantage of the benefits associated with being first to market. Such disclosures could have the unintended consequence of eliminating many small device companies from the marketplace and could have a negative long-term impact on patient access to innovative technologies.

In addition, protocols are often hundreds of pages in length and may quickly over-burden the data bank. Protocols will also be uniquely formatted according to the sponsor's standards making clarity and transparency challenging for the public. In conclusion, we support FDAAA's purpose of providing transparent and complete information to the public on clinical trials and we believe – in keeping with the current structure of ClinicalTrials.gov – the full listing of data elements referenced above presents understandable information that is consistently formatted for comparison purposes and that does not reveal confidential or proprietary information of device sponsors.

- 5. Procedures the agency might consider for quality control, with respect to completeness and content of clinical trial information, to help ensure that data elements are not false or misleading and are non-promotional. Consider the effect of different approaches on the workload of both data submitters and the agency and on the quality of data available to the public, as well as suitable means for the agency to communicate information about its quality assurance processes to data submitters and the public.**

AdvaMed Response

With respect to the first part of Question 5, AdvaMed concurs that reports of clinical trial data elements should not be false, misleading or promotional. We would note that existing law (Section 502 of the FDC Act) prohibits manufacturers from disseminating false or misleading product information which would include false or misleading clinical trial information. In addition, FDA regulations prohibit manufacturers from promoting an investigational device (21 C.F.R. §812.7). FDA already applies these standards to clinical trial information that is provided by manufacturers in written materials, such as press releases about clinical trial results and press releases about advisory panel decisions on PMA submissions. Since manufacturers are familiar with, and are currently held to these legal standards, we do not believe new quality control requirements or procedures or guidance are necessary for postings on ClinicalTrials.gov. Of course, it will be important for FDA and NLM to ensure consistent interpretation and implementation of these existing regulatory requirements across and within the Agencies when these

requirements are applied to materials posted on the data bank, such as technical and non-technical summaries of trial results.

With respect to the second part of Question 5, concerning suitable means for the Agency to communicate information about its quality assurance processes to data submitters and the public, AdvaMed appreciates that ClinicalTrials.gov has posted a Draft Quality Assurance/Quality Control Review document for public review. Transparency of this information is very useful to sponsors entering information into the data bank.

- 6. Whether the 1-year period for submission of basic results information should be increased to a period not to exceed 18 months. Comment on the advantages and disadvantages of increasing the period for submission of clinical trial information from 1-year after the completion date to a period not to exceed 18 months. Consider the implications for all stakeholders, including governmental bodies, data submitters, and users of ClinicalTrials.gov; the extent to which such a change would affect public health or the utility of the data bank; the possible effect on the number of requests that responsible parties would submit to the NIH requesting an extension of the results reporting deadline; and the possible improvements to the quality and or completeness of initial submissions of results data to the NIH. Consider the implications of delay periods of different lengths between 12 and 18 months.**

AdvaMed Response

AdvaMed supports expanding the one year period for submission of basic results information to 18 months from the “Primary Completion Date” as allowed for in FDAAA. Some secondary outcomes may require longer-term follow-up data on the primary outcomes (e.g., mobility functional score at 12 months where the primary outcome measured the same outcome at 3 months). This means many trials are incomplete at the time basic results are now required to be entered by FDAAA due to planned secondary outcomes. As a result, analysis at the point in time now required by FDAAA for submission of “basic results” introduces a “partial or additional database lock” process which requires verification of the data in the database (i.e., complete data monitoring and resolution of data queries), analyses, validation of the analyses, and interpretation of results. Expansion to 18 months reflects a more reasonable timeframe to complete these critical processes so as to meet the basic results reporting requirements, and to ensure that the most complete data are available for posting. This may also minimize the number of requests for “good cause” extensions to complete data analysis.

Further, we believe a common timeframe for updating secondary results and for providing technical and non-technical summaries (which should include complete information on primary and secondary outcomes) would provide clarity to trial sponsors and to the public on when such updates are expected. By design it is common for a clinical trial to be ongoing for secondary endpoint data collection after the “Primary Completion Date” and even following the time when basic results are due. An update

process may cause confusion as the required updates may appear to be ad hoc updates versus planned data collection.

For updating results related to secondary outcomes and for providing technical and non-technical summaries, AdvaMed proposes the timeline should be 18 months following the “Study Completion Date” (i.e., last data collected for primary and secondary outcomes on last subject) as defined in the data bank Protocol Data Element Definitions document (August 20, 2008 draft). We interpret “Study Completion Date” (versus “Primary Completion Date”) as the final date on which all primary and secondary data were collected on the last study subject. This may or may not be the same date as the “Primary Completion Date” depending on the scientific protocol design.

This proposed 18 month timeline provides clarity and consistency where secondary outcomes may be later than primary outcomes (e.g., specified health outcomes at 12 months where the primary outcome measured the same outcomes at 3 months). It allows sufficient time to accomplish data verification and analysis processes that drive quality reporting of data presented in the summaries. It enables a reasonable timeframe for presenting information to the public while recognizing the complexity of the continuum of clinical trial designs. In addition, this timeline minimizes the need for “good cause” extensions as well as updates and modifications to the results information, thus reducing confusion to users of the data bank.

Please see AdvaMed’s response to Question 9, section “g.” for suggested additions to data elements in the data bank that will assist users in understanding the results status of a particular trial.

- 7. Whether the clinical trial information required by the regulation should be required to be submitted for applicable clinical trials for which “basic results” information is submitted before the effective date of the regulation. Consider the advantages and disadvantages to data submitters and users of the data bank, including patients, prospective human subjects, care providers, and researchers.**

AdvaMed Response

AdvaMed believes it is too burdensome for both sponsors and ClinicalTrials.gov staff to require sponsors to submit data for all the likely expanded data elements that will be required by the new rule for clinical trial entries that were entered prior to the effective date of the regulation. Such a requirement may cause an extensive backlog of results data requiring review and will result in a significant delay in release of results to the public. Although FDAAA specifically asks ClinicalTrials.gov to review the possibility of requiring expanded results for trials entered prior to the effective date, we would also point out that applying regulations retroactively is contrary to typical legal standards of due process which favor prospective rather than retroactive application.

- 8. The appropriate timing and requirements for updates of clinical trial information and procedures for tracking such updates. Please comment on the advantages and disadvantages of requiring more frequent updating of information submitted to the clinical trial registry and results data bank, which elements (if any) would benefit from more frequent updating, and what would be the optimal frequency of such updates.**

AdvaMed Response

Please see the AdvaMed response to Question 6 for our comments on the appropriate timing for updates of clinical trial information.

- 9. The standard format for the submission of clinical trial information required by the regulation, including adverse event information, and additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of the FDAAA.**

AdvaMed Response

Section 801 of FDAAA directs ClinicalTrials.gov to expand basic results reporting to serious and frequent adverse event (AE) information by regulation within 18 months of enactment. If the Secretary fails to issue AE reporting regulations in this area by 24 months after date of enactment, FDAAA establishes two default statutory reporting requirements or data elements for AEs (Section (j)(3)(H)(I)(ii) and (iii)): Serious Adverse Events (all anticipated and unanticipated SAEs grouped by organ system); and Frequent Adverse Events (anticipated and unanticipated AEs that are not included in the SAE section) that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system.

In order to enhance patient understanding and to ensure such Adverse Event sections do not mislead patients, AdvaMed recommends improvements to the statutory AE default reporting requirements as implemented on ClinicalTrials.gov described below. AdvaMed also has recommendations on Additions or Modifications to Basic Results Data Elements.

- a. Adopt the ISO 14155 definition of Serious Adverse Effect for use in reporting Serious Adverse Events for medical devices.
- b. Replace “Other (Not Including Serious) Adverse Events” with “All (Including Serious and Non-Serious) Frequent Adverse Events.”
- c. Include an additional “AE Reporting Criteria” data element.
- d. Include additional data elements that will describe whether the adverse event is attributed to the medical device.
- e. Calculate percentages automatically.
- f. Require entry of “Number of Participants at Risk” once per study arm, rather than repeating it for every AE term.
- g. Recommendation on additions or modifications to basic results data elements.

Further details regarding these recommendations and the rationale for such are included below:

a. Adopt the ISO 14155 Definition of Serious Adverse Effect (SAE) For Use in Reporting Serious Adverse Events for Medical Devices

Section 801 of FDAAA directs NLM to expand basic results reporting in ClinicalTrials.gov to serious and frequent adverse event (AE) information. As you are aware, the regulations on adverse event reporting for drugs and devices differ. The recently released FDA Guidance on Adverse Event Reporting to IRBs³ highlights the differences between drugs and devices in reporting requirements as well as in terminology and criteria for evaluation. For example, the Investigational New Drug (IND) regulations define “serious adverse drug experience”⁴. The Investigational Device Exemption (IDE) regulations on the other hand, refer to the term “serious” in “unanticipated adverse device effects” reporting requirements⁵, but do not provide a definition. Thus, there may be some variation in how “serious” is defined for trial-specific or protocol-driven reporting purposes.

During the April 20, 2009 public meeting on Section 801 of FDAAA, NLM and FDA asked AdvaMed whether the definition of serious adverse event contained in the March 9, 2009 Draft “Basic Results” Data Element Definitions document adequately captured medical device serious adverse events. After careful consideration, AdvaMed recommends that NLM and FDA incorporate the international standard ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects) definition for Serious Adverse Effect into the basic results data element definitions document for medical device serious adverse event.

ISO 14155 defines a Serious Adverse Effect (SAE) as an adverse event that:

- led to a death
- led to a serious deterioration in the health of the subject that
 - resulted in a life-threatening illness or injury, or
 - resulted in a permanent impairment of a body structure or a body function, or
 - required in-patient hospitalization or prolongation of existing hospitalization, or
 - resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

³ See FDA Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs -- Improving Human Subject Protection (January 2009) available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf>.

⁴ See 21 CFR 312.32

⁵ See 21 CFR 812.150

Use of the ISO 14155 definition will ensure a harmonized approach to capturing SAEs in medical device trials, many of which are conducted outside of the United States. Additionally, we believe this definition will be more readily understood by medical device trial sponsors and will be consistent with the way they currently collect SAEs. Please see the Comparison Table in Appendix A that compares adverse event definitions that are used by medical device manufacturers to the AE definitions currently in ClinicalTrials.gov and to the IND regulation AE definitions.

b. Replace “Other (Not Including Serious) Adverse Events” with “All (Including Serious and Non-Serious) Frequent Adverse Events”

As stated previously, the default statutory language of FDAAA for adverse events requires two sections: SAEs (see comments in previous section 9. “a.”) and Frequent AEs. The Frequent AE section is defined by statutory requirements to exclude Serious AEs and as such, ClinicalTrials.gov has renamed the “Frequent AE” section as the “Other (Not Including Serious) Adverse Events” section.

AdvaMed recommends replacing the current “Other (Not Including Serious) Adverse Events” section with a requirement to report “All (Including Serious and Non-Serious) Frequent Adverse Events” exceeding a threshold of 5 percent. By doing so, NLM would ensure that the public is provided with accurate information regarding the most frequent AEs. An example illustrating this point is provided below.

Example

One cannot derive the frequency of all adverse events by adding the two adverse events sections (e.g. “Serious” + “Other (Not Including Serious)” AEs).

- 10 patients (of 100) reported a serious event X (e.g., headache).
- The same 10 patients also reported a non-serious event X (e.g., headache) at a different time.
- Current ClinicalTrials.gov requirements would reflect the AE reporting as follows:
 - 10 of 100 (or 10%) reported a serious event X (e.g., headache).
 - 10 of 100 (or 10%) reported an “Other (non-serious)” event X (e.g., headache).
 - What is the frequency of event X?
 - If the public assumed that no patient reporting a serious event X (e.g., headache) had also reported a non-serious event X (e.g., headache), they would assume a frequency of 20%. By adding the serious and non-serious event Xs together, it would appear that 20 of 100 patients experienced event X.
 - If the public assumed the same 10 patients that reported a serious event X (e.g., headache) also reported a non-serious event X (e.g.,

headache), they would assume a frequency of 10% or that 10 of 100 patients experienced event X.

- The Issue: Under the default statutory language, the public does not have enough information to determine the frequency of event X.
- The solution: AdvaMed recommends reporting "All (Including Serious and Non-Serious) Frequent Adverse Events" at a frequency above a 5% threshold.

c. *Include an Additional "AE Reporting Criteria" Data Element*

To ensure AE information is interpreted in the context of trial-specific reporting criteria, AdvaMed also proposes that FDA and NLM add a new text data element, "AE reporting criteria", to the structure of AE reporting in ClinicalTrials.gov to enable sponsors to report any trial-specific AE definitions (e.g., "MAE," "MACE," and "MACCE"⁶) where it may be critical to interpreting the results information. Character limits should not exist in this field to allow sponsors to directly copy applicable portions of the study protocol. For example, the therapeutic area, study product (e.g., drug, device, drug and device [combination product]), stage or phase (e.g., phase I-IV, or feasibility, pivotal, post-market), and the trial's scientific design (e.g., blinded) will drive the trial-specific requirements for adverse event reporting. Additionally, for many large post-market trials (both drug and device), where the adverse event profile of the products under study have been well-documented in product labeling, the trial may focus only on the collection of "serious" and unexpected adverse events. This approach is intended to minimize data collection and reporting burden where collection of all adverse events (e.g., grade I sinus infections) would not benefit the study or clinical care. In this case, a post-market study may not collect AEs, and therefore, will have no "frequent AEs" unless spontaneous study reports result in new information.

Thus for many appropriate reasons, each specific trial may have individual AE reporting criteria. This makes it challenging for someone to compare reported adverse events across studies without providing the context of the trial-specific reporting criteria, and in some cases, trial-specific definitions (e.g., "serious"). AdvaMed believes the addition of the new text data element, "AE reporting criteria," will enable AE results information to be "useful and not misleading to patients, physicians, and scientists" as contemplated by FDAAA.

⁶ MAE – Major Adverse Event is defined as events related to the product and/or procedure (e.g., death, myocardial infarction, repeat revascularization, stent thrombosis, stroke) and is further defined in the protocol; MACE – Major Adverse Cardiac Event is defined as events related to the product and/or procedure (e.g., death, myocardial infarction (Q wave and non-Q wave), emergent bypass surgery, or repeat target lesion revascularization; and MACCE – Major Adverse Cardiac and Cerebrovascular Event is defined as events related to the product and/or procedure (e.g., death, myocardial infarction, cerebrovascular accident or repeat revascularization by percutaneous intervention or bypass surgery).

d. *Include Additional Data Elements That Describe Whether an AE is Attributable to the Medical Device*


AdvaMed also recommends the addition of data elements that enable those who use the data bank to understand the context of AEs. In the case of devices, it is important to evaluate safety information in the context of attribution to the device and/or the procedure (e.g., implant surgery) to fully evaluate the benefit-to-risk ratio. This allows for evaluation of incremental or comparative risk between devices that are implanted with the same or similar procedure. Also, the complexity of combination products (those regulated as a device would be reported per device study requirements) may require additional attribution categories to be specified (e.g., drug). While attribution may be debated, the information on attribution provided by the investigator closest to the situation and/or a committee of experts (e.g., data safety monitoring committee, AE committee) provides useful information to patients and physicians evaluating the results of the study. We propose incorporating the ability to assign attribution to each AE type in the tabular structure. Attribution categories for devices should include: device/system, procedure, other (specify: e.g., drug if applicable, patient co-morbidities or other medical conditions). See Table B below which is intended to help illustrate our recommendations.

e. *Calculate Percentages Automatically*

AdvaMed also proposes that percentages should be automatically calculated or requested and presented in AE tables for reporting on proportional data. The current data bank structure leads sponsors to enter the total sample size in each group, along with the number of events, or subjects in a particular event category. The public or other users of the data bank may make incorrect conclusions about a comparison if percentages are not presented in the AE tables. A person quickly looking at a study where 400 subjects were randomized to treatment A with 100 experiencing adverse events, and 200 were randomized to control with 90 experiencing adverse events might make a direct comparison of 100 to 90 and conclude that treatment A was less safe. The explicit presentation of proportions or percentages is more meaningful for interpretation (e.g., 25% in treatment A group and 45% in the control group in this example). See Table B below.

f. *Require Entry of “Number of Participants at Risk” Once Per Study Arm*

ClinicalTrials.gov requires the entry of “number of participants at risk” for each adverse event term reported. Since the “Number of Participants at Risk” may vary for each study arm/group but will not vary for each adverse event term, AdvaMed recommends allowing the “Number of Participants at Risk” to be entered once per study arm, rather than repeating the entry for each unique adverse event term. See Table B below.

Table B: Mock AE Table Including Relatedness Categories						
Adverse Events	Group X # participants at risk	Group Z # participants at risk	Determined Related to: (Y/N)			
			Device / System	Procedure (Implant)	Other (specify: xxxxxx)*	Other (specify: xxxxxx)*
Total, Serious AE # of events # participants affected %	XXX XX X%	XXX XX X%				
Event A # of events # participants affected %	XX XX X%	X X X%	Y	N	N	N/A
Event B # of events # participants affected %	X X X%	X X X%	N	Y	N	N/A

* **Note:** allow multiple “other (specify:)” columns to accommodate different study designs as currently allowed in reporting by group (e.g., only adjudicated to device or implant; adjudicated to device, implant, drug X, or patient co-morbidities/medical conditions)

g. Recommendations on Additions or Modifications to Basic Results Data Elements

With respect to additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of FDAAA, AdvaMed recommends a new results data element (e.g., checkbox or drop-down menu option) that would enable companies to explain to data bank users the following situations:

- The trial was voluntarily registered prior to the FDAAA effective date and results posting is not legally required.
- The trial is an applicable trial and results are required to be submitted.
- The trial is not an “applicable clinical trial” and was entered into the registry on a voluntary basis and results posting is not legally required.
- The trial is completed and the device is FDA cleared or approved but results are not required to be posted at this time.
- Primary results only have been entered.
- If applicable, secondary results will be entered 18 months following study completion date (i.e., final date on which all primary and secondary data were collected on the last study subject).
- The trial was stopped for reasons unrelated to safety and will have no results to post.

- The trial is completed and the device is pending FDA clearance or approval. Therefore, results are not required to be posted at this time.

We also propose that an additional data element be added to disclose when secondary data and technical and non-technical summaries are anticipated (based on scientific study design and 18 months following “Study Completion Date”).

Finally, in actual practice, the format for the submission of clinical trial information and especially the manner of reporting results is not user-friendly and is very burdensome for those who must input data. In particular, it is awkward if the data don't fit into the standard categories that are provided. Given the wide variability in device products this is not an infrequent occurrence. The XML option is not useful for non-IT users who must input the data at many companies. AdvaMed recommends that the data bank be expanded to allow sponsors to upload Word or Excel tables, rather than manually entering data field-by-field. The current techniques are also burdensome for the ClinicalTrials.gov Quality Assurance (QA) group and lay audiences because they do not result in concise presentation of data. We believe that the ability to upload tables in Word or Excel could simplify the process for all users.

10. A statement to accompany the entry for an applicable clinical trial when the primary and secondary outcome measures for such clinical trial are submitted as a “voluntary submission” after the date specified in the FDAAA for submission of such information.

AdvaMed Response

As discussed in AdvaMed’s response to Question 9, section “g.” regarding “additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of the FDAAA,” we believe that the addition of a new results data element (e.g., checkbox or drop-down menu option) that explains to databank users various situations would be useful. Please see our suggested additions in “g.” in Question 9 above.

11. Other issues associated with Section 801 of the FDAAA that will inform rulemaking.

AdvaMed details a number of implementation concerns and our associated recommendations below:

- a. Create waiver for delayed disclosure.
- b. Rely on existing FDA definitions of devices subject to Sections 510(k), 515, and 520(m).
- c. Establish formal extension process.
- d. Clarify in guidance factors that will be considered when applying civil or criminal penalties.

- e. Clarify in guidance that results are never due sooner than 12 months after last subject seen for primary outcome.
- f. Provide opportunity to comment on draft NLM guidance via Federal Register process.
- g. Clarify registration requirements in guidance for observational IVD trials ensuring consistency with Section 801 of FDAAA and with existing FDA regulations and practices.

a. *Create Waiver for Delayed Disclosure*

As you know, AdvaMed supported the inclusion of language in FDAAA providing for “delayed disclosure” of device clinical trial registry information to ensure that such information is posted publicly in the registry data bank not earlier than the date of clearance or approval and not later than 30 days after such date (Section (j)(2)(D)(ii)(I)). We supported this provision on behalf of our companies, particularly smaller device companies, in order to protect and maintain the competitiveness of the device industry and continued innovations for patients by ensuring that sensitive, confidential commercial information would be protected from public disclosure until after FDA approval or clearance. Unlike the drug industry where entire molecules are patented (and are frequently patented even before the first clinical trial begins), patents provide little protection in the device industry because competitors can easily negate device patents with simple engineering or design changes. Disclosure of the existence of an IDE through the data bank could provide significant advantages to competitors who could potentially speed a competing device into clinical trials and obtain FDA clearance or approval in order to take advantage of the benefits associated with being first to market. Such disclosures could have the unintended consequence of eliminating many small device companies from the marketplace. Small companies account for a vast number of device innovations for patients and contribute greatly to maintaining strong price competitiveness across the industry.⁷ In many instances, small companies are willing to invest in developing technologies for niche and orphan markets – patient communities that may otherwise be overlooked.

FDA and NLM have implemented the delayed disclosure language by requiring device companies to first indicate whether the trial is an “applicable” device trial, then whether delayed posting applies. This approach is appropriate for companies that desire protection from disclosure of their clinical trial information until after the device is cleared or approved, per FDAAA. However, some device

⁷ A 2008 study found that overall prices of medical technology grew more slowly than either the Medical Consumer Price Index (MCPI) or the Consumer Price Index (CPI) in the 15-year period ending in 2004. Over the same period, medical technology has accounted for a relatively low and constant percentage of total national health expenditures. Roland King & Gerald F. Donohue, *Estimates of Medical Device Spending in the United States*, 3-4 (Advanced Medical Technology Association, 2008).

companies are willing to disclose clinical trial information prior to FDA clearance or approval in order to ensure publication in peer review journals that follow ICMJE guidelines. In this latter case, companies have been advised by NLM and FDA to either provide inaccurate information that the device trial is not subject to delayed disclosure or to leave the question blank. In the first instance, the government is advising companies to provide inaccurate information to ClinicalTrials.gov. Similarly, in the second, the government advises companies to provide incomplete information to ClinicalTrials.gov.

AdvaMed recommends that FDA and NLM create an additional option in the data bank that indicates the trial is an applicable device trial for which the manufacturer seeks no delays on public disclosure of the registry data in order to meet ICMJE requirements. FDA and NLM should make clear in accompanying instructions the differences in the options.

AdvaMed retained outside counsel to provide a legal assessment of whether NLM can register and list clinical trial information for a device that has not been previously marketed prior to the approval or clearance of the device if waived by the device submitter. AdvaMed's legal assessment is attached in Appendix B.

We understand that some journals who are members of ICMJE have – paradoxically – indicated they will penalize device companies who comply with the law. As a result, device manufacturers seeking to meet the *non-statutory* requirements of some ICMJE member journals are forced to choose between two options: leave the checkbox blank or declare that the trial is not an applicable device trial.

It should be noted that AdvaMed communicated with Dr. Harold Sox, Editor of the *Annals of Internal Medicine*, in advance of the June 2008 ICMJE meeting to propose a potential solution on the delayed disclosure issue. We made the assumption that some ICMJE representatives believed that device industry compliance with the delayed disclosure provision Section (a)(2)(D)(ii)(I) would affect a journal's ability to assess whether a device sponsor had appropriately registered a device trial. We proposed that the unique National Clinical Trial (NCT) number assigned by ClinicalTrials.gov provides evidence that a sponsor has indeed registered the trial as required. The NCT number could be included in the cover letter of a manuscript submission, thereby demonstrating trial registration. We continue to believe this approach represents a resolution to this issue.

b. Rely on Existing FDA Definitions of Devices Subject to Sections 510(k), 515, and 520(m)

In a December 8, 2008 draft guidance, NLM elaborates on the statutory definition of “applicable device clinical trial.” In this draft, NLM further describes what is intended by the element “a device subject to 510(k), 515, or 520(m) of the Federal

Food Drug and Cosmetic Act.” In doing so, the draft guidance proposes that the criteria for determining whether or not a device is subject to 510(k), 515, or 520(m) is “where the device being used in the clinical study is manufactured.” This new criteria changes the current statutory requirements defined in sections 510(k), 515, or 520(m) of the FDC Act. To define device 510(k), 515, and 520(m) requirements in this manner has implications well beyond clinical trial registration, extending to areas such as product application/submission and manufacturing requirements.

It is not uncommon for U.S. companies to manufacture devices in the U.S. that are intended for export only with no intent to market the device in the U.S. The NLM guidance implementing clinical trial registration and results posting should not alter the statutory requirements for these devices through statements that such devices are subject to 510(k), 515, and 520(m).

Sections 510(k), 515, and 520(m) of the FDC Act clearly define when a device is subject to one of these provisions. That is, when one proposes to begin the introduction or delivery for introduction of the device into interstate commerce for commercial distribution. Because the statutory provisions 510(k), 515, and 520(m) clearly define when a device is subject to one of these sections it is unnecessary to redefine these provisions in the context of clinical trial registration and results posting. By redefining these provisions in a manner contrary to long-standing understanding and interpretation, new requirements are established where they did not exist before.

To redefine these sections whenever they are referenced in a statutory provision has the potential to result in multiple definitions and confusion.

Consistent with long-standing understanding and interpretation, AdvaMed recommends continued reliance on the existing definitions of devices subject to sections 510(k), 515, and 520(m) in the context of Section 801 of FDAAA.

c. Establish Formal Extension Process

FDAAA allows for delayed submission of results information with certification where the sponsor is seeking initial approval or clearance of a product or approval or clearance of a new use for an existing product. Additionally, FDAAA allows the Director of NIH to provide an extension of the deadline for submission of results information where the responsible party demonstrates good cause for the extension in a written request and provides an estimate of the date on which the information will be submitted. NLM has provided “Temporary Instructions for Certification or Request for Extension” directing the responsible party to provide specific information in an e-mail to register@clinicaltrials.gov with “Certification or Extension Request” in the subject line. AdvaMed appreciates that NLM provided these temporary instructions and understands there is an ongoing effort

to establish and implement a formal process. We would like to request NLM replace these Temporary Instructions with the following process:

- Certifications or requests for extensions should be made through the ClinicalTrials.gov data bank. To implement this automated process, NLM should add new data elements to input the certification or request and connect it to the specific trial registration information (i.e., under or prior to the Results Information tab).
- NLM responses to certifications or requests for extension should be sent to the submitter through the automated response system that is currently in use on the ClinicalTrials.gov database that notifies a submitter when NLM has made an edit to one of the submitter's records.
- NLM responses to certifications or requests for extensions should be posted on the ClinicalTrials.gov data bank so that the information is made public to ensure transparency and to minimize any perception of non-compliance in the timing of results information submission where delays or extensions have been approved.

In addition, we suggest that NLM develop guidance to provide information on the process used to review certifications or requests for extensions, the criteria used to approve or deny a request for extension, and identify operational groups responsible for making these decisions.

We also urge NLM to include a process for "reconsideration" in the event that a request for extension is not approved to ensure the responsible party has the opportunity to provide additional information or resolve any potential misinterpretation of information.

d. Clarify in Guidance Factors That Will Be Considered When Applying Civil or Criminal Penalties

FDAAA placed new strict liability prohibited acts that relate to conduct under the registry and results data bank requirements in Section 301 of the FDC Act. This could subject device companies to significant penalties for minor omissions or inadvertent errors in data entry.

Strict liability is a very exacting standard that we do not believe was intended to apply to data entry of multiple layers of highly technical clinical trial information. In determining whether to apply a penalty under this subsection for a violation of Section 301(jj), AdvaMed requests that FDA and NLM clarify in guidance that they will consider "intent" such as:

- whether the responsible party promptly corrects the noncompliance when provided notice;
- whether the responsible party has engaged in a pattern or practice of noncompliance; or

- the extent to which the noncompliance involved may have significantly misled health care providers or patients concerning the safety and effectiveness of the device involved.

e. Clarify in Guidance That Results Are Never Due Sooner than 12 Months After Last Subject Seen for Primary Outcome

Based on interactions with NLM and FDA, we understand that clinical trial results are never due sooner than 12 months after the final subject was seen for the primary outcome even though the device may have been cleared earlier. In response to Question 6, AdvaMed supports expanding the 12 month timeframe to 18 months. In either case (i.e., a 12 month or 18 month timeframe), AdvaMed concurs with NLM that one timeframe should be consistently used to ensure that posted results reflect the complete analysis and to minimize the number of requests for good cause extensions. AdvaMed recommends that NLM clarify these points in guidance using examples.

f. Provide Opportunity to Comment on Draft NLM Guidance Via Federal Register Process

AdvaMed recognizes and appreciates that NLM has developed draft guidance to assist sponsors and others in complying with and understanding the FDAAA clinical trial data bank requirements and that this draft guidance is available for informal comment on the ClinicalTrials.gov website. We recognize that this informal process is helpful to share early drafts of NLM's thinking on how to proceed with aspects of a challenging and complex system, to "work out the kinks." We appreciate having this opportunity and would like it to continue. However, to ensure transparency, we believe that before finalizing such guidance, it is important that the broadest possible audience is made aware of the draft guidance documents and of the process for submitting comments on them. For these reasons, AdvaMed recommends that NLM follow a guidance process that utilizes traditional mechanisms for public distribution and comment i.e., a Federal Register Notice and a minimum 60-day comment period process prior to finalizing draft guidance documents. Such a comment process would also be consistent with FDA's Good Guidance Practices (GGP).

g. Clarify Registration Requirements in Guidance for Observational IVD Trials Ensuring Consistency with Section 801 of FDAAA and with Existing FDA Regulations and Practices

AdvaMed recommends that NLM clarify clinical registration requirements and guidance regarding observational device studies, such as most *in vitro diagnostic* (IVD) device studies, to ensure consistency with Section 801 of FDAAA as well as FDA's existing regulations and practices. AdvaMed supports providing full and complete clinical trials registry information of applicable device trials under Section 801. Information issued to date on observational trials, such as *in vitro* diagnostic studies, however, has been confusing. Most IVD studies merely compare the performance of a device to another existing device and are non-

interventional with no direct impact on patients. FDA has historically treated most IVD studies as observational and has distinguished them from interventional trials.

FDAAA is clear that there must be an intervention with a device to be an applicable device trial. Further, FDAAA recognizes that some types of trials are not applicable device trials, such as feasibility studies. Similarly, IVD non-interventional studies do not constitute applicable device trials. Based on the well-established FDA regulatory framework for IVD devices and other device studies where the devices do not have direct impact on patients, such studies are observational studies. Consistent with the definition under FDAAA, these types of non-interventional studies are not applicable device clinical trials.

For IVD and other observational studies, it is also important to distinguish the intervention at issue from ancillary procedures. For example, for IVD device studies, the blood draw is done merely to obtain specimens for use in the device study—the blood draw is not the intervention that the clinical study is designed to evaluate (i.e., the purpose of the study is not to evaluate whether the blood draw is safe and effective). The blood draw is merely a procedure done to collect a routine sample with the purpose of evaluating the diagnostic device.

FDA's treatment of such observational studies is well-established, including recognition of the non-interventional characteristics of most IVD studies. For example, the FDA's Investigational Device Exemption (IDE) regulations under 21 CFR § 812.2 (c)(3) and CFR § 812.3 (k) specifically exempt certain IVD studies from IDE regulation on the basis of minimal risk to the subject from whom samples are collected and the fundamental characteristics of such studies, in particular the impact on the subject. Most IVD studies are exempt because the studies are noninvasive (i.e., blood sampling involves simple venipuncture); the study sampling procedure does not present significant risk (e.g., provision of urine, stool, swab, or blood samples) and does not introduce energy into a human subject, and the results are generally not used to diagnose a patient or, in the rare event that the result is used by a physician, it cannot be used without confirmation by other, medically established diagnostic products or procedures.

As mentioned, most IVD studies simply compare the performance of a device to another existing device. IVD device study results are often not even provided to health care providers or used in patient management. Even in instances when results are available to health care providers, in most cases the results of the investigational diagnostic device are prohibited from being used to treat or diagnose a patient. Furthermore, the health care provider is often using a similar, FDA-cleared IVD device within the accepted standard of care.

Consistent with Section 801 and FDA's regulatory framework, interventional trials (which includes certain IVD trials) where results directly impact patient care

are subject to registration. In the case of studies with IVD devices where results (per study protocol) are provided to the health care professional or to the patient to assign treatment options or are used as a sole determinate to assign subjects to treatment or control groups, AdvaMed agrees these trials are interventional in nature and constitute “applicable clinical trials” under Section 801.

During the April 20, 2009 public meeting, FDA asked AdvaMed to provide examples to better understand the types of IVD clinical trials that meet the definition of applicable device clinical trial and that require registration. To illustrate our points, below we provide the following examples of both interventional and observational IVD studies:

a) Examples of Interventional IVD Clinical Trials (That Require Registration)

- i)** Subjects enrolled in a study to provide blood specimens for assessing clinical specificity of an IVD device (also referred to as an IVD “test”) and determining the assay cutoff are provided study results and asked to consent for a follow-up blood draw. The specimens are prospectively collected. If specimen results fall into a particular range of values, the subjects are called back and given feedback on their study results and asked to consent for a follow-up blood draw. Here there is an intervention with a device because the subject is provided information about the test result and because there is direct impact on the patient (follow-up testing) as a consequence of the device’s result. Therefore, we believe this study is an applicable device clinical trial. (Note: This study would be conducted with FDA oversight under an IDE or Investigational New Drug Application (IND)).
- ii) **Subjects are enrolled in a study for a new blood donor screening test for a**** parasitic or infectious disease with no previously licensed comparator assay. The clinical trial protocol is conducted under an IND and requires informed consent from the donor for collection and testing of the blood sample. Testing performed on the blood donor sample with the investigational assay is positive. Confirmatory testing is performed on the same blood sample using a licensed confirmatory test or unlicensed reference test. The blood donor is deferred from future blood donations based on the results of the investigational assay and confirmatory result and the current blood donation is not released into blood inventory. In this example, the donor receives the study results and is referred to a private physician for consultation and possible treatment. Because the subject is provided information about the test result and there is direct impact on the patient (the patient is referred for medical consult), we believe such study is an applicable device clinical trial.

- iii) Subjects are enrolled in a study to determine safety and potential for improved efficacy of lowering the diagnostics cutoff for a tumor marker assay. The current standard of care requires ultrasound and biopsy for antigen detection with results greater than 4.0 ng/ml. The study requires follow-up ultrasound and biopsy for subjects with results showing greater than 3.0 ng/ml. In this example, there is an intervention (ultrasound and biopsy) for patients with results between 3.0 and 4.0 ng/ml. Because the tests results have an impact on this subset of patients, the study should be classified as an applicable device clinical trial. (Note: This study would be conducted with FDA oversight under an IDE).

b) *Examples of IVD Observational Studies (Would Not Require Registration)*

- i) Subjects are enrolled in a study to provide blood specimens. The specimens are prospectively collected, but no investigational test results are given to the subjects or to the subjects' physicians. The medical history and test results will be used in assessing clinical sensitivity and clinical specificity of the IVD device and determination of the assay cutoff. In this example, there is not an intervention with a device because the device does not have an impact on patient care. This study would not be an applicable device clinical trial.
- ii) Subjects are enrolled in a study evaluating a licensed or approved test that is modified. The objective of the study is to confirm the already approved performance characteristics of the device as they appear in the labeling. (Note: These studies most often use direct comparison with a previously approved or cleared IVD device.) Patient intervention based upon the use of the test result from the IVD device is not possible or is specifically prohibited as test results are not linked to the actual donor. The objective of the protocol is to conduct a statistical comparison to the licensed/approved test. This study would not be an applicable device clinical trial.
- iii) Subjects are enrolled in a study to evaluate a new investigational tumor marker assay. Subjects are enrolled prospectively and their medical history and test results will be evaluated to ensure the investigational assay meets FDA expectations for safety and effectiveness. Test data for a previously cleared IVD device will also be obtained and the investigational device results will be compared with those from the cleared device. Subjects will receive standard care and no investigational data will be used in the care of the subject, although results from the previously cleared device will be used as current standard of care. Here again, there is no intervention with the device and no impact on patient care as a result of the device. This study would not be an applicable device clinical trial.

- iv) Subjects are enrolled in a study to determine the safety and effectiveness of raising the diagnostic cutoff for a tumor marker assay. The current standard of care requires ultrasound and biopsy for antigen detection with results greater than 3.0 ng/ml. The study requires that the follow-up ultrasound and biopsy information, which would be otherwise conducted for the patient, be collected for patients with results between 3.0 and 4.0 ng/ml. The ultrasound and biopsy information will be compared to the entire population to determine if ultrasound or biopsy for patients with results between 3.0 and 4.0 ng/ml should be indicated. There is no intervention with the device because there is no additional activity with the patients that affect care. Because there is no intervention with the subject, the device does not have an impact on patient care. This study would not be an applicable device clinical trial.
- v) Subjects are enrolled in a study to determine the usability of a new IVD device that has not been cleared in order to support validation of a design change for human factors improvement. There is no control group. Each subject enrolled in the study is using the device, which is similar to a previously cleared device. There is no comparison of different interventions. This study would not be an applicable device clinical trial.

In sum, as illustrated by the above examples, most IVD studies merely compare the performance of one IVD device to another existing IVD device and do not have a direct impact on patients. In most cases, IVD device study results are never provided to the health care provider or used in patient management. Under FDA's longstanding regulatory framework for IVD devices, such studies are observational, not interventional. Consistent with FDAAA and FDA regulatory requirements pertaining to IVD studies, IVD interventional device trials where there is an impact on the patient as a consequence of the device results (e.g., protocol calls for additional treatment intervention or referral for follow-up testing or physician consult for a patient subset) are applicable clinical trials and should be registered.

AdvaMed recommends that NLM guidance recognize that observational IVD clinical studies, which are non-interventional studies, are not applicable device clinical trials under Section 801 and that NLM provide examples of both observational IVD studies that do not require registration and interventional IVD trials that do require registration. AdvaMed retained outside counsel to provide a legal assessment in this area. AdvaMed's legal assessment is attached in Appendix C.

Deborah A. Zarin, M.D.
June 22, 2009
Page 316 of 38

In conclusion, thank you for your consideration of AdvaMed's comments on issues the Agency will consider as it develops regulations to expand the clinical trial registry and results data bank as well as additional areas of concern to device manufacturers associated with implementation of Section 801. Please don't hesitate to contact me if you have any questions.

Sincerely,

A handwritten signature in cursive script that reads "Tara Federici".

Tara Federici
Vice President
Technology and Regulatory Affairs

Appendix A

Comparison Table on “SERIOUS” Adverse Event or Effect Definitions: Events that lead to or result in . . .

ClinicalTrials.gov: <u>Serious Adverse Event</u>	21 CFR Part 312 (IND Regulations): <u>Serious Adverse Drug Experience</u>	21 CFR Part 812 (IDE Regulations): <u>Unanticipated Adverse Device Effect</u> – The following events when caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence. . .	21 CFR Part 803 (Medical Device Reporting for Marketed Devices): <u>MDR Reportable Event and Serious Injury</u>	ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects): <u>Serious Adverse Effect</u>
Death	Death	Death	Death or serious injury	Death
Inpatient hospitalization or the prolongation of hospitalization	Inpatient hospitalization or prolongation of existing hospitalization			Inpatient hospitalization or prolongation of existing hospitalization
Life-threatening	Life-threatening	Life-threatening	Life-threatening	Life-threatening illness or injury
Persistent or significant disability/incapacity	Persistent or significant disability/incapacity		Permanent impairment of a body function or permanent damage to a body structure	Permanent impairment of a body structure or a body function
Congenital anomaly/birth defect	Congenital anomaly/birth defect			Foetal distress, foetal death or a congenital abnormality or birth defect
Other important medical events, based upon appropriate medical judgment . . . if a trial participant’s health is at risk and intervention is required to prevent an outcome as mentioned	Important medical events . . . based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition	Serious Adverse effect on health or safety NOTE: Does not define “serious”	Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure	Medical or surgical intervention to prevent permanent impairment to body structure or a body function
			(Device) has malfunctioned and . . . would be likely to cause or contribute to a death or serious injury if the malfunction were to recur	

Appendix B

Outside Counsel Legal Assessment

Waiver of Delayed Posting of Device Clinical Trial Information

Question Presented

Can NIH post information from an applicable device clinical trial prior to the approval or clearance of a device that has not been previously cleared or approved by FDA under Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), when the device sponsor requests that the clinical trial information be posted in NIH's Clinical Trial Registry Data Bank?

Short Answer

Yes, the device sponsor should be able to waive the statutory requirement that delays the posting of clinical trial information until after a device is cleared or approved by FDA.

Discussion

The law governing the clinical trial registry states that

[t]he Director of NIH shall ensure that clinical trial information for an applicable device clinical trial submitted in accordance with this paragraph is posted publicly in the registry data bank –

(I) not earlier than the date of clearance under section 510(k) of the Federal Food, Drug, and Cosmetic Act, or approval under section 515 or 520(m) of such Act, as applicable, for a device that was not previously cleared or approved, and not later than 30 days after such date....

42 U.S.C. § 282(j)(2)(D)(ii)(I) (emphasis added). This delayed posting requirement was created to protect device submitters of 510(k)s and PMAs from premature disclosure of confidential commercial information that is protected from disclosure under FDA's regulations. Specifically, FDA will not disclose the existence of a pending premarket submission under most circumstances. *See, e.g.,* 21 C.F.R. § 807.95(b) (stating FDA "will not disclose publicly the existence of a premarket notification submission for a device that is not on the market and where the intent to market the device has not been disclosed for 90 days from the date of receipt of the submission..."); 21 C.F.R. § 814.9(b) ("The existence of a PMA file may not be disclosed by FDA before an approval order is issued to the applicant unless it previously has been publicly disclosed or acknowledged."). Maintaining this protection was particularly important for devices that had not been previously cleared or approved by FDA, and the delayed posting was limited to these devices.

Creating the delayed posting provision balanced the desire for public awareness of clinical trials with the need to protect device innovators' confidential commercial information related to the development of new devices. The delayed posting provision ensures that the

confidentiality of a company's product development is maintained by restricting the posting of clinical trial information until after approval or clearance when the existence of the new device becomes public.

Because this delayed posting provision is intended to protect the confidential information and interests of the potential marketer, *i.e.*, the person potentially submitting a 510(k) or PMA, the 510(k) or PMA submitter should be in a position to waive the delayed posting if that is the submitter's preference, assuming the waiver would not interfere with the purpose of the registry data bank legislation. For example, if the device sponsor would need to register its trial with NIH as a condition to publication of its clinical trial results,⁸ delayed posting would be a detriment not a benefit to the sponsor. Indeed, inflexibly refusing to publicly acknowledge the registration of a clinical trial, thus precluding its publication in the medical literature when registration with the data bank is a publication prerequisite, would frustrate the intent of Section 801, *i.e.*, to make clinical trial information publicly available for patients and physicians.

A sponsor's interest in posting its clinical trial in the registry data bank earlier than after the device's approval or clearance is entirely consistent with the intent behind the clinical trial registry, namely to share clinical trial information with the public.⁹ Thus, if a device sponsor wishes to waive the right to delayed posting, the statutory language prohibiting the earlier posting should not be understood as a bar to a consensual disclosure of a clinical trial. Indeed, not only would the waiver of delayed posting make available the statutorily required data bank information, but it could result in the publication of trial results in the medical literature, thus providing another means of distributing information about new devices. Under circumstances where a party wishes to waive a statutory right, and that waiver would not frustrate the public purpose of the statute, courts have acknowledged that statutory rights intended to protect individual rights may be waived by the persons for whom the statute provides protection.¹⁰

Additionally, the Supreme Court explained in the context of construing a statute that broad statutory language should not be read to result in an outcome at odds with the spirit of the law. The Court stated:

⁸ See <http://prsinfo.clinicaltrials.gov/> ("ClinicalTrials.gov facilitates registration of trials in accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical trials in a public registry as a condition for publication.").

⁹ See, *e.g.*, 153 Cong. Rec. S11831 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) ("A second major element of our legislation is a public registry of clinical trials and their results. A complete central clearinghouse for this information will help patients, providers and researchers learn more and make better health care decisions. Now, the public will know about each trial underway, and will be able to review its results."); 153 Cong. Rec. H10551, H10596-97 (daily ed. Sept. 19, 2007) (statement of Rep. Markey) ("[A] mandatory clinical trial registry and results database... will ensure that the public has accurate and complete information about drugs and devices. This bill will create that mandatory clinical trials database.").

¹⁰ See, *e.g.*, *Canal Electric Co. v. Westinghouse Electric Co.*, 406 Mass. 369, 378 (1990) ("A statutory right or remedy may be waived when the waiver would not frustrate the public policies of the statute.").

[F]requently words of general meaning are used in a statute, words broad enough to include an act in question, and yet a consideration of the whole legislation, or of the circumstances surrounding its enactment, or of the absurd results which follow from giving such broad meaning to the words, makes it unreasonable to believe that the legislator intended to include the particular act.

Public Citizen v. United States Department of Justice, 491 U.S. 440, 454 (1989) (quoting *Church of the Holy Trinity v. United States*, 143 U.S. 457, 459 (1892)). In *Public Citizen*, the Supreme Court found the Federal Advisory Committee Act (FACA) did not apply to the American Bar Association's Standing Committee on Federal Judiciary (ABA Committee), when the President, through the Justice Department, requested the ABA Committee's advice in nominating federal judges. Although FACA defines an advisory committee to be a committee "utilized" by the President or an agency, the Court found if it "[r]ead [the word "utilized"] unqualifiedly, it would extend FACA's requirements to any group of two or more persons, or at least any formal organization, from which the President or an Executive agency seeks advice." 491 U.S. at 452. The Court concluded Congress never intended such a result.

In the current situation, the intent behind the delayed posting provision was to benefit the person submitting the 510(k) or PMA for a new device; an inflexible reading of that provision would punish the submitter and frustrate the purpose of the registry data bank law, which was to make clinical trial information available to the public at the earliest reasonable time. Under these circumstances, a waiver of the delayed posting provision "would not frustrate the public policies of the statute" *see Canal Electric Co.*, 406 Mass. at 378. Moreover, permitting early posting is consistent with FDA's own disclosure regulations, which permit FDA to disclose the existence of a 510(k) or PMA if the sponsor has already publicly acknowledged its existence. *See* 21 C.F.R. § 807.95(a)(2); 21 C.F.R. § 814.9(b).

NIH recognizes that registrants of device trials often want their clinical trial information promptly posted and not delayed until after receipt of clearance or approval. To accommodate such requests NIH in the past instructed registrants to check the box on the registration form indicating that the device was previously approved or cleared by FDA. *See* ClinicalTrials.gov Protocol Data Element Definitions (DRAFT) (Aug. 20, 2008), <http://prsinfo.clinicaltrials.gov/definitions.html>. By doing so, the delayed posting of clinical trial information would not be applicable to the device trial. However, NIH's advice would result in incorrect statements to the government. NIH understands its form and past recommendation created a conundrum for itself and device sponsor registrants, and now recommends that registrants not answer the question as the means to avoid delayed posting. This approach creates some of the same concerns as counseling registrants to make incorrect statements.

In sum, we believe that the Director of NIH could fairly interpret the statute to permit waivers of the delayed posting of device clinical trials. Interpreting the statute this way would avoid placing NIH in a position where it is counseling registrants to submit incomplete forms or to make incorrect statements. A far preferable approach for the government and device sponsors would be for NIH to release a new form that permits a waiver election.

Appendix C

Outside Counsel Legal Assessment

Applicability of FDAAA Clinical Trial Registry Requirements to Non-Interventional IVD Studies

Question Presented

Are non-interventional studies on *in vitro* diagnostic (“IVD”) devices “applicable device clinical trials” under section 801 of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”)¹¹?

Short Answer

No. IVD studies that are non-interventional do not meet Section 801’s definition of applicable device clinical trials and do not need to be registered.¹² Because such non-interventional studies do not impact patient care, their registration would not serve the purpose of Section 801 to enhance patient access to, and information on, experimental therapies.

Analysis

FDAAA subjects “applicable device clinical trials” to the enhanced clinical trials registry requirements. Among other things, to be an applicable device clinical trial, the trial must compare an “intervention with a device” against a control. The statute does not define the phrase “intervention with a device”, so in interpreting this language, we look to statutory intent and purpose, other relevant sources of law, and commonly accepted definitions of such terms. These authorities persuade us that an “intervention with a device” requires that the IVD device being studied impact the subject’s care, diagnosis, or treatment.

IVD device studies often do not have such an impact on human subject participants. For example, such studies often focus on assessing the performance characteristics of the IVD and do not inform any patient diagnosis or treatment. As a result, IVD studies will often not meet the statutory definition of an “applicable device clinical trial” because they do not involve an “intervention with a device,” which is a key element under the statute.

¹¹ Enacted at 42 U.S.C. § 282(j).

¹² Importantly, the converse – that interventional IVD studies are required to be registered – is not necessarily true. Interventional IVD studies and other device studies may also not meet the definition of applicable device clinical trials for other reasons, such as not having a control. This could be the case, for example, in a study of an IVD device that is focused on the usability features of the IVD. The subjects or their caregivers may even use the results, but because the focus is on the user features of the IVD device, there may be no control. In this case, the study would not be an applicable device clinical trial even though there was an invention (i.e., patient impact) with the device.

At the outset, understanding the patient-focused objectives of the clinical trial registry requirements enacted by FDAAA is important. Specifically, the central objectives of Section 801 include (a) providing patients and healthcare providers with information on and access to enrollment in clinical trials for experimental therapies and (b) providing safety and efficacy information to the public.¹³ As discussed below, requiring registration of non-interventional studies that by definition do not impact patient care would not fulfill those purposes of the FDAAA requirements.

1. *To be subject to FDAAA's enhanced registration requirements, a device clinical trial must compare an "intervention with a device" to a control.*

Section 801 of FDAAA sets forth enhanced registration requirements for "applicable device clinical trials." The statute defines an "applicable device clinical trial" as "a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects." The statute also sets forth certain exceptions to this definition, such as feasibility studies. While there are several important elements to this definition, this memorandum is largely focused on the phrase "intervention with a device." To state that phrase another way, device trials requiring registration must be "interventional," in addition to meeting the other statutory requirements.

Before discussing the meaning of "intervention," we first want to be very clear on the phrase as a whole.

- a. *The intervention at issue for purposes of registering the clinical trial is an intervention "with the device."*

At the outset, it's important to recognize that the "intervention" at issue for registering the clinical trial is an "intervention with a device" – not an intervention with ancillary procedures that may be used in the research. For example, in IVD studies, if a blood draw is done merely to obtain specimens for use in research, the blood draw is not the intervention that the clinical study is designed to evaluate -- *i.e.*, the purpose of the study is not to evaluate whether the blood draw is safe and effective. The blood draw is merely a procedure done to evaluate the diagnostic test. The question is whether there is an intervention with the diagnostic test.¹⁴ The statutory language is clear on this point.

¹³ See H.R. Rep. No. 110-225, at 12, 49 (2007); See also FDA, *Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff: Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007* (Jan. 2009).

¹⁴ We can conceive of a situation (though admittedly far-fetched) in which the blood draw itself might be the "intervention." Consider a clinical trial designed to compare a blood draw with some alternative procedure for collecting specimens from a person (e.g., as a mouth swab). The subjects are divided into two groups. The intervention group would have their blood drawn; the control group would give a swab of tissues from their mouths. The purpose of the study would be to decide whether it is safer and more effective to do a blood draw

The NIH recognized this distinction in its draft protocol data element definitions document issued in August 2008. Specifically, in considering whether a trial is an “applicable clinical trial”, the document first poses the question of whether the trial concerns an “FDA regulated intervention” (i.e., a drug or medical device). Thus, the question is whether there is an intervention with the studied device – not ancillary procedures such as blood draws. Further, additional questions about whether a trial is an “applicable clinical trial” only come into play if the answer is “yes” to an FDA-regulated intervention.

In another context, ClinicalTrials.gov has defined interventions as follows:

“INTERVENTION NAME: The generic name of the precise intervention being studied.

INTERVENTIONS: Primary interventions being studied: types of interventions are Drug, Gene Transfer, Vaccine, Behavior, Device, or Procedure.”¹⁵

Thus, the statutory language and the agency interpretations are clear that, in order for a study to potentially qualify as an applicable device clinical trial, there must be an intervention with the device that’s being studied. Next we turn to what, in fact, is an “intervention” – i.e., what impact must the device have?

b. To have an “intervention with a device”, there must be some impact on patient care.

The statute does not define “an intervention with a device”. As a result, we must be informed by other sources of authority. In this regard, well-accepted definitions of a clinical trial illustrate that in order to have an “intervention,” there must be some impact on the patient. For example:

“A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings.... A clinical trial must employ one or more *intervention* techniques. These may be ‘prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures, etc.’ Intervention techniques should be applied to participants in a standard fashion in an effort to change some aspect of the participants.”¹⁶

as opposed to taking a swab. In this hypothetical, the blood draw itself would be the “intervention” that is being evaluated.

¹⁵ ClinicalTrials.gov, *Glossary of Clinical Trials Terms*, available at: <http://www.clinicaltrials.gov/ct2/info/glossary#diagnostic> (last accessed June 4, 2009).

¹⁶ Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets, *Fundamentals of Clinical Trials* (3rd ed., 1998, Springer Science + Business Media LLC) (Emphasis added).

Another example is found in the International Committee of Medical Journal Editors' ("ICMJE") definition of clinical trial:

"Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes)."¹⁷

And another example from a registry focused on a particular condition:

"In an interventional trial, the investigators give the participants a particular investigational drug or other intervention, which may include a gene transfer, vaccine, device, or procedure, such as surgery. The intervention may or may not be assigned randomly, and sometimes treated individuals might be compared with those who receive no treatment. The researchers then measure how the health of the participant changes. Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective."¹⁸

All of these definitions have in common a focus on the intervention changing or modifying a health outcome. Applied here, to be considered under the statutory test, the device being studied would need to be applied in such a way to "change" the research subjects.

Most IVD studies do not meet this definition because the device being studied has no effect on the patients – the device is not used to impact or influence any patient treatment, diagnosis, or outcome. Results of studied IVDs often are not even provided to a healthcare professional or the patient because most IVD studies simply compare performance results produced by the investigational device to existing devices – not on an individual basis. As a result, IVD study results are generally not used to diagnosis or treat a patient. Further, as discussed above, this can be true even if the study happens to make use of blood or tissue specimens that were taken for prospective use in the study via ancillary procedures, such as a blood draw or other form of clinical intervention with a patient.

This interpretation of the non-interventional nature of most IVD studies is consistent with the FDA regulatory framework for IVD studies. For example, the FDA's investigational device exemption regulation specifically exempts certain IVD studies from IDE regulations, on the

¹⁷ ICMJE, *Frequently Asked Questions About Clinical Trials Registration*, available at <http://www.icmje.org/faq.pdf> (last accessed June 5, 2009); see also ICMJE, *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors* (Sept. 2004). (Emphasis added.)

¹⁸ PDtrials, available at <http://www.pdtrials.org/en/browse/type/10/1> (last accessed June 5, 2009). PDtrials is a collaborative initiative of Parkinson's organizations dedicated to increasing education and awareness about clinical research. (Emphasis added.)

basis of risk and the fundamental characteristics of such studies.¹⁹ Under the regulations, in order to be exempt from IDE requirements, the study must meet the following criteria: (i) Is noninvasive,²⁰ (ii) Does not require an invasive sampling procedure that presents significant risk, (iii) Does not by design or intention introduce energy into a subject, and (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.²¹ Thus, FDA regulations recognize that IVD studies that do not impact patient care (or indeed, even have a risk-managed impact on patient care) are different from other studies.

In sum, when IVD study results are not used in patient management, there simply is no intervention with the device. Moreover, this interpretation is consistent with the underlying intent and purpose of the FDAAA requirements in enhancing patient access to, and information on, experimental therapies. Registration of IVD studies that do not involve the use of test results in patient treatment or diagnosis is not needed to serve the purpose of the FDAAA requirements.

2. *Current drafts of interpretive documents do not address this fundamental consideration of impact on patient care in defining applicable device clinical trials.*

As we all know, the implementation of the enhanced clinical trials registry requirements has resulted in a greatly increased workload for NIH and FDA, and they have been under pressure to interpret and implement the requirements in a short timeframe. Unfortunately, this time crunch seems to have resulted in some inconsistent or incomplete guidance.

One such example is in the draft elaborations document issued on March 9, 2009.²² In discussing applicable device clinical trials, this document recognized the unique considerations involving research on banked samples, as described in the FDA's guidance on studies involving the use of de-identified banked samples.²³ We agree that this is an important distinction.

On the other hand, the document also seems to infer that research on samples that are not de-identified necessarily constitutes applicable device clinical trials. However, the use of de-identified versus identified samples is not the determinative factor for deciding whether a

¹⁹ 21 CFR § 812.2(c).

²⁰ The IDE regulations provide that blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive. 21 CFR § 812.3(k).

²¹ 21 CFR § 812.2(c)(3). (Emphasis added.) Of course such studies can impact a patient if the test result is communicated to the caregiver with the confirmatory test. We are not suggesting that all tests that meet this definition are excluded from the registry, rather simply that FDA acknowledges the uniqueness of IVD studies.

²² ClinicalTrials.gov, Protocol Registration System, *Elaboration of the Definition of Responsible Party and Applicable Clinical Trial*, pp. 4-5, 6, available at:

<http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf> (last accessed June 4, 2009).

²³ FDA, *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff* (Apr. 25, 2006).

trial is interventional. In other words, a study can be subject to human subject protections yet not subject to registry requirements. A visual depiction may help illustrate this point.

	IVD STUDY DESCRIPTION	Do human subject protections, such as informed consent, apply?	Is there an intervention with the IVD device under FDAAA registry requirements?
1	Study of IVD device using de-identified samples	No ²⁴	No, by definition the IVD study does not involve an intervention with a device
2	Study of IVD device using identifiable samples; results do <u>not</u> impact care of subject	Yes	No, the IVD study does not involve an intervention with an investigational device (i.e. the test, not the venipuncture) that impacts care
3	Study of IVD device using identifiable samples; results impact care of subject	Yes	Yes, there is an intervention (i.e., impact on the subject) with the device being studied

In effect, the current draft of the elaborations document does not address study 2 in the table, in which informed consent and other requirements apply, yet registry requirements do not apply to the IVD study because there is no intervention with the IVD device.

As another example of problematic guidance, the ClinicalTrials.gov resource page currently provides as follows:

“Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. ClinicalTrials.gov includes both interventional and observational types of studies. *Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators.*”²⁵

²⁴ See *id.*

²⁵ ClinicalTrials.gov, *Understanding Clinical Trials*, available at: <http://www.clinicaltrials.gov/ct2/info/understand> (last accessed June 4, 2009).

This definition is overly simplistic and fails to fully define interventional trials. It is also problematic because it fails to recognize that, in order to potentially be subject to registration requirements, a device clinical trial must be interventional, in addition to meeting other statutory requirements.²⁶

In all, to be consistent with the statutory language of FDAAA, documents implementing and interpreting the FDAAA registry requirements should clarify the definition of applicable device clinical trials and recognize the important distinction between intervention and non-interventional device studies, particularly in the context of studies on IVD devices.

Conclusion

In summary, when considering whether an IVD clinical study has an “intervention with a device,” two points are important. One, the invention at issue is an intervention with the IVD device that’s being studied. Two, an intervention means there must be some impact to patient care with the IVD device. If the use of the IVD device being studied does not impact patient care, there’s not an intervention with the IVD device under FDAAA.

In the context of IVD studies, the device being studied is often not being used in a manner that impacts patient care. Much of IVD research – and not just research using de-identified samples – does not involve an intervention with the IVD device. This interpretation is consistent with the purpose of the FDAAA requirements, other definitions of clinical trials, as well as FDA requirements for IVD research.

²⁶ Of course, responsible parties may choose to register studies that do not meet the definition of applicable device clinical trial.



200 First Street SW
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March 22, 2015

Re: Comments on Proposed Rule: Clinical Trials Registration and Results Submission

Docket Number: NIH-2011-0003
RIN number: 0925-AA52

To Whom It May Concern:

Thank you for the opportunity to comment on the National Institutes of Health's (NIH) Notice of Proposed Rulemaking (NPRM) for Clinical Trials Registration and Results Submission. We agree on the importance of disseminating results of publically funded research to contribute to the general body of scientific knowledge, and providing acknowledgement and respect to the contributions of the subjects who have taken part in research.

Mayo Clinic supports many of the proposed requirements for registration and results reporting, however we do want to point out the complexities facing academic researchers in navigating the various definitions and requirements between NIH, FDA, ICMJE, and the ClinicalTrials.gov system.

We wish to submit the following comments and suggestions for your consideration when finalizing the proposed rule. Excerpts of the relevant NPRM text are in bold, followed by our comments for items 1-6 in our response letter. Items 7-10 are more general in nature with examples provided.

1. III. Overview of Proposed Rule, C. Key Issues, 7. Submission of the full protocol (FR 69582).

We believe this proposal would be redundant as the registration and results data elements currently required provide sufficient information for both public awareness and compliance. If this proposal would go into effect, protocol redaction standards would need to be developed and followed, adding unnecessary burdens.

2. III. Overview of Proposed Rule, C. Key Issues, 6. Submission of non-technical and technical summaries of trial results (FR 69581).

Regarding the proposal to post summaries, we believe this would be an unnecessary burden and if required, we would need to have really clear and concise standards on what is expected. As well, HHS or NIH would need to ensure that these summaries would not be considered "prior publication" by ICMJE and individual journals.

3. III. Overview of Proposed Rule, C. Key Issues, 1. Elaboration of statutory definitions (FR 69574). An algorithm would replace the sponsor's determination of applicable status (currently answered by Y/N question, "Section 801 Clinical Trial?")

We recommend consideration be given for the ability to override this algorithm with documentation to justify a study is not an applicable clinical trial to demonstrate compliance with the law, and to avoid fines and/or penalties. As an example: the current functionality of the ClinicalTrials.gov database will capture as applicable clinical trials device feasibility studies. We would like the ability to have a data field to respond why a study is not an ACT.

Part 11, Subpart B, Section 11.22 (b): Determination of applicable clinical trial. (FR 69671)

We would like to know if there will be any appeal process established if the responsible party disagrees with the algorithm that the study is an applicable clinical trial. If not currently planned, we recommend this be considered as you are setting up the system.

4. III. Overview of Proposed Rule - D. Effective Date/Compliance Date (FR 69593). In situations when partial results are due on or after the effective date of the rule to require the responsible party to submit clinical trial results information for all outcome measures, including primary outcome measures submitted prior to the effective date of the rule.

Updating previously approved outcome measures that have passed NIH/PRS quality review may present a significant burden for investigators. Considering that studies completed prior to the effective date were not designed or budgeted to comply with the new requirements, some investigators may be unable to comply. Attempting to comply or explaining why compliance is not possible will be very time-consuming to investigators, PRS administrators at the institution, and PRS reviewers.

5. VI. Regulatory Impact Statement (FR 69655)

The NPRM document estimates that to register a study, it would take approximately 8 hours, and to update the record over the life of the study, it would require 2 hours per update. In addition, for studies requiring the submission of results data, an estimated additional 40 hours are expected. For an investigator with little experience or infrequent experience with the ClinicalTrials.gov application, these estimates might be too short, and the burden of compliance could be heavy. For the NIH policy, the addition of additional studies to register could create a greater burden of work for physicians already taxed by their clinical and research duties.

6. Subpart C – Results Submission Section 11.48 (FR 69676) (summary)

The NPRM proposes that responsible parties submit "the total number of participants affected by an adverse event by the organ system." Many Academic Medical Centers (AMCs) do not have an institution-wide system for data collection. MedDRA coding is not standard for AMCs and the Body Organ System Class is assigned manually only at the time of ClinicalTrials.gov data entry. This creates an additional burden, with potential for errors in manual counting. If the organ-system field is not recorded as part of normal study conduct, it would have to be added to each AE entry at the time of results reporting. If an investigator is fortunate to have IT support, a summary report of the organ system field would be created that would then have to be entered into ClinicalTrials.gov manually. Studies active as of the effective date, and those that are completed with results in preparation, have not budgeted for the resources needed to comply with additional programming and reporting requirements. Our recommendations would be to not require organ-system for non-industry/AMC sponsor-investigator AE

reporting. At most, make this proposed requirement voluntary. Note: since the number at risk for the arm is likely to be the number at risk for each organ system, we suggest that the number at risk “by organ system” defaults to the number at risk for the entire treatment arm.

- 7. Subpart A – General Provisions Section 11.4 (3) (FR 69667) (summary) (i) In the event that a PI who has been designated as the responsible party (RP) becomes unable to meet all the requirements, the PI must withdraw the designation as specified by ClinicalTrials.gov, at which time the sponsor will be considered the responsible party until the sponsor makes a new designation. (ii) In the event a PI who has been designated the RP is unable because of death or incapacity to withdraw his or her designation, the sponsor will be considered the RP until the sponsor makes a new designation.**

We suggest the sponsor be allowed to remove the RP designation if the PI leaves the institution. Sometimes this occurs without much warning, and there is no time to transfer the study and the study data to another PI. In addition, we suggest the sponsor could submit a waiver of results requirements if studies have been terminated and only partial results (if any) were obtained. We have had some instances of studies being abandoned due to the death or relocation of the PI. It can be at best, very time consuming to impossible to find the data to enter the results for these cases, creating an unnecessary burden on the institution.

8. Consistency of Timelines/Deadlines:

We recommend consideration be given to provide consistency in timelines/deadlines within the proposed rules. A mixture of 30-day and 15-day response/requirements increases the complexity of the rule-making and makes compliance more difficult. We strongly encourage a standard 30-day window (requirement) for all deadlines; shorter windows do not seem to provide any additional benefit for compliance and will only complicate expectations for investigators, particularly those who are infrequent users of the system.

Examples include:

- Quality Control Procedures [FR 96584] – Proposes that RP correct errors within 15 days of notification by NIH, or by becoming aware of them, whichever is earlier.
- Section 11.44 (a)(2) – [FR69674] Extension for submitting results. After denial notice, results are due within 15 calendar days. Also see Section 11.44 (e)(3).
- Section 11.54 (a) (4) – [FR 69677] Waiver request. RP needs to submit by original deadline or 15 days after denial notice is sent.
- Section 11.54 (b) (1) RP may appeal denial letter within 15 calendar days.
- Section 11.66 (a) [FR69680] Correction of Errors. Must correct within 15 days of becoming aware of errors. Same time frame for subsequent sections: Section 11.66(b) falsified data and Section 11.66(c) other corrections.

9. Burden for Academic Medical Centers (non-industry)

The proposed rule along with the proposed NIH policy will create significant burdens for AMC and their investigators. We, along with many other AMCs, are already expending considerable resources to support compliance with FDAAA results reporting requirements. AMCs support a large number of physician-investigators who are accountable for information entered in the ClinicalTrials.gov database. These individuals, along with those who support them face additional complexities in navigating the various requirements from FDAAA, NIH, and NLM (ClinicalTrials.gov). Consideration should be given to either “grandfather in” trials that are already in

progress, or delay the implementation date to allow for changes to the Protocol Registration System to better accommodate AMCs.

10. Terminology and Clarification

Examples include:

- **Part 11, Subpart A, Section 11.10: What Definitions apply to this part? (FR 69668) “Completion Date” will now be used instead of “Primary Completion Date.”** This new terminology will be confusing to the responsible parties. Currently NLM and NCI definitions of Completion Date do not agree. How will Secondary Outcome Measure Completion Dates be tracked, as no field has been proposed to collect this? We suggest that the NLM retain the use of “Primary Completion Date,” since the concept that a study is “Completed” but still can be “Active, Not Recruiting” seems mutually exclusive, and that alternately clear definition of Primary Completion Date could fulfill the same purpose.
- **Part 11, Subpart A, Section 11.10: (FR) “Study Start Date means the estimated date on which the clinical trial will open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled.** We suggest harmonization with other definitions, for example, ICMJE. We consider studies to have “started” when they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled. ClinicalTrials.gov could call this field “Date of First Enrolled Participant,” instead of “Study Start Date.”
- **Part 11, Subpart D, Section 11.62 (a) (FR 69678) RP has received notification that the Director has determined that posting of clinical trial information for an ACT is necessary to protect the public health.** We would like to know the criteria used by the Director of NIH to determine that a study is “necessary to protect public health.” Also, under what circumstances would this apply, retrospectively to studies already completed? Would this apply to studies that were voluntarily registered?

11. Additional fields required (instead of optional)

Examples include:

- **Part 11, Subpart A, Section 11.10: What Definitions apply to this part? (FR 69669) Sponsor (14) US FDA Approval, Licensure, or Clearance Status.** This will be a new field that requires sponsors to enter the status of approved, licensed, or cleared by the US FDA for any use for each drug or device. We would suggest that approval status for the indication be an available option, e.g., “approved but not for use being studied.” As an academic medical organization, we often are studying drugs and devices for new indications.
- **Part 11, Subpart A, Section 11.10: What Definitions apply to this part? (FR 69669) Sponsor (15) Product manufactured in the US.** This new data element will be required to assist in determining if a study is an ACT. We would like to request clarification if a drug or device is just packaged or labeled in the US qualifies as being “manufactured in the US?” If packaging and labeling is included, this would require an additional burden of research for academic medical organizations, since we do not manufacture the products studied.
- **Part 11, Subpart D, Section 11.64(vi) (FR 69679) Individual Site Status must be updated no later than 30 calendar days after a change in status of any individual site.** We would like to comment that this could create a burden to track

and update site information on an individual basis, especially for large multicenter studies.

As we recognize the need for the public to be made aware of results of clinical trials, we request consideration of balancing regulatory requirements with the benefits expected from the proposed rule. Our Mayo Clinic Protocol Registration System (PRS) Administrators currently oversee over 1200 records on ClinicalTrials.gov. Based on our own significant experiences, completing results reporting in the national database (ClinicalTrials.gov) as currently established takes considerable resources and time for our investigators and staff.

We respectfully submit these comments for your consideration and thank you for the opportunity to comment on this proposed rule.

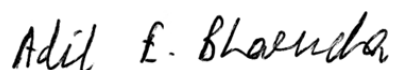
Sincerely,



Gregory Gores, M.D., F.A.C.P.
Kinney Executive Dean for Research
Reuben R. Eisenberg Professor of Medicine and Physiology
Mayo Clinic



Sundeep Khosla, M.D.
Dr. Francis Chucker and Nathan Landow Research Professor
Principal Investigator and Director, Mayo Clinic Center for Clinical and Translational Science
Mayo Clinic



Adil Bharucha, MBSS, M.D.
Professor of Medicine
Chair, Clinical Trials Subcommittee and Chair, Research Compliance Subcommittee
Mayo Clinic

From: [Shandi Barney](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Cindy Tomlinson](#)
Subject: ASTRO comment letter on clinical trial policy
Date: Monday, March 23, 2015 8:47:06 AM
Attachments: [Comment letter Clinical trial rule LT.PDF](#)

Good morning,

Please see the attached comment letter from ASTRO on the proposed rule on the NIH policy for clinical trials. Let me know if you have any questions.

Thanks!

Shandi

Shandi E. Hill
Manager of Congressional Relations
American Society for Radiation Oncology
8280 Willow Oaks Corporate Drive, Suite 500
Fairfax, VA 22031
703-502-1550 main
703-839-7382 direct
703-474-0940 cell
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www.astro.org
www.rtanswers.com

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March 20, 2015

Francis S. Collins, MD, PhD
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

RE: Proposed rule and draft policy on clinical trials transparency (Docket number NIH-2011-0003)

Dear Dr. Collins,

The American Society for Radiation Oncology (ASTRO), representing more than 10,000 radiation oncology medical professionals who treat more than 1 million cancer patients each year, commends the National Institutes of Health (NIH) for its commitment to enhance transparency around clinical trials to ensure that researchers, physicians and patients receive the most comprehensive and current information available.

As the leading organization in radiation oncology, biology, and physics, ASTRO is dedicated to the advancement of the practice of radiation oncology by promoting excellence in patient care, promoting and disseminating research results and representing radiation oncology in a rapidly evolving healthcare environment. ASTRO believes that increasing transparency around the use of federal research funds and clinical trials will result in an increase in trial participation and expand the impact and value of the contributions made by trial participants, ultimately getting us one step closer to a cure for cancer. As the NIH continues to strengthen the transparency of how federal funds are allocated, ASTRO urges NIH to address the disparity in funding for radiation oncology research and reallocate funds to ensure that this critical cancer treatment receives the support it needs.

ASTRO supports the requirement for information submitted to www.clinicaltrials.gov to be provided in a structured format to ensure that it is user friendly for researchers, physicians and patients. Additionally, ASTRO supports the proposed rule's requirement that all applicable trials-- not just those for which the devices studied are FDA approved, licensed, or cleared-- report results about existing treatments and those in development. Doesn't make sense? Seems like it is missing something we strongly urge the NIH to make sure that the data be as accurate and up-to-date as possible.

As you know, ASTRO has demonstrated longstanding support for NIH and cancer research, and is committed to urging Congress to support NIH so that we can continue on a path of accelerating advances in cancer care.

We appreciate the opportunity to provide you with feedback on your proposals, and we look forward to working with you improve the quality and efficiency of health care, while protecting

access to life-saving cancer care for all Americans. Please feel free to contact Shandi Barney, IS TRO's congressional relations manager at (703) 839-7382 with any questions.

Sincerely,

Laura I. Thevenot
Chief Executive Officer

From: [Montillo, Karen J.](#) on behalf of [Orf, Harry W.,Ph.D.](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: MGH_Response to NIH policy_3.20.15'
Date: Monday, March 23, 2015 9:01:06 AM
Attachments: [MGH_Response to NIH policy_Clinical trials registration_3 20 15.pdf](#)

MGH_Response to NIH policy_3.20.15'

Thank you for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019.)*

I am writing on behalf of the Massachusetts General Hospital (Mass General). Please see attached document.

Harry W. Orf, PhD | Senior Vice President for Research

Massachusetts General Hospital | Bulfinch 240E
55 Fruit Street | Boston, MA 02114
617.724.9079 | horf@mgh.harvard.edu

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Harry W. Orf, Ph.D.
*Senior Vice President for Research
Massachusetts General Hospital
Principal Associate in Genetics
Harvard Medical School*

March 19, 2015

RE: NOT-OD-15-019: NIH Draft Policy on Clinical Trials Registration and Results Reporting

Thank you very much for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019)*. I am writing on behalf of the Massachusetts General Hospital (Mass General), a principal teaching affiliate of Harvard Medical School.

The Mass General is the third oldest general hospital in the United States and the original and largest teaching hospital of Harvard Medical School. A founding member of Partners HealthCare System, Mass General conducts the largest hospital-based research program in the U.S, encompassing both basic science and clinical research, and is consistently ranked among the top two hospitals nationally receiving NIH funding. In FY 14, Mass General received approximately \$350 million in research funding from the NIH. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to the Mass General research enterprise.

While we support the NIH's expectations and efforts to make research and results information publicly available, we are concerned that the proposed policy without clarification and revision would impose a significant administrative burden on investigators and institutions and lead to confusion over interpretation of requirements. Thus, based on our experience administering a large and diverse clinical trials research program and meeting current clinical trials registration and results reporting requirements, we respectfully offer recommendations we believe would assist the NIH in developing a clear and coherent policy.

NIH Definition of clinical trial and the effect on registration and reporting requirements

We acknowledge NIH's new definition of clinical trial to determine whether a NIH funded clinical trial requires registration and results reporting. We appreciate that NIH has elaborated on certain terms within the definition (e.g. 'prospectively assigned', 'intervention') and published FAQs and case studies. Of note, we find the case studies particularly helpful and would welcome publication of additional case studies over time.

However, it is important to recognize that when the NIH policy and the simultaneously issued FDAAA NPRM become effective, investigators conducting PI-initiated research will need to navigate four different clinical trial definitions and registration criteria: the FDAAA definition of Applicable Clinical Trial, the NIH definition of clinical trial, the ICMJE definition of clinical trial,

and the CMS definition of qualifying clinical trial. These definitions of clinical trial each differ or appear to differ from one another, in some cases in subtle ways; the associated timelines for registration and overall responsibilities (results reporting, updating the record) differ across some (but not all) of these sources of rules. In our experience, investigators are frequently confused by these various requirements and a good deal of effort and resources are required to assist them in understanding their responsibilities.

In order to support institutions and investigators in understanding and reconciling the various definitions and requirements, we strongly recommend that the NIH collaborate with FDA, ICMJE and CMS to harmonize definitions to reduce or eliminate differences. If this is not possible, we recommend a joint effort to publish guidance comparing and contrasting all requirements for clinical trials registration and results reporting. Differences in definitions should be explicitly articulated and highlighted with case studies.

Clarity with regards to privately funded studies using NIH Infrastructure

The Scope and Applicability section of the proposed NIH policy asserts that the policy'... applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the FDAAA registration and results submission requirements set forth in Section 4020} of the Public Health Service Act (42 U.S.C. 2820)).'

We suggest clarification regarding privately funded studies using NIH infrastructure. We note that National Cancer Institute Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials (Notice Number: NOT-CA-15-001, release date 1/28/15) defines *NCI-Supported Clinical Trials* as follows: '...all clinical trials financially supported - whether in whole or in part - by the NCI. Clinical trials that are wholly funded by private entities (and in which the data from the clinical trial belong to the private funder) are not considered to be NCI-supported even if such studies are conducted at the NCI-designated Cancer Centers and benefit from the Cancer Center infrastructure.'

The clarification that privately funded trials using NCI supported infrastructure are not covered as part of the NCI policy is a significant detail that helps academic centers understand the scope of the policy. Clinical and Translational Science Awards (CTSA) set up infrastructure at academic institutions similar to the NCI-designated Cancer Centers. We request the Scope and Applicability section of the proposed NIH policy insert similar language which provides helpful clarity regarding privately funded studies using CTSA infrastructure.

Required results reporting for behavioral clinical trials

We appreciate that the ClinicalTrials.gov database has undergone many revisions to accommodate different types of research including behavioral and observational research. The NIH proposed policy to require results reporting of behavioral clinical trials will now include investigators who have no experience with the results database. We note that ClinicalTrials.gov

has examples of studies for results data entry (parallel study design, cross-over study design, etc). These examples have been very helpful to the academic research community. We recommend that NIH, in collaboration with ClinicalTrials.gov, publish additional examples specific to behavioral study design.

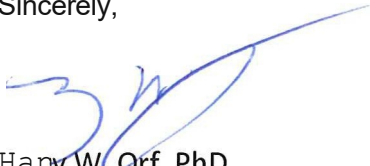
Compliance with policy

The NIH draft policy does not provide specific information on certain key aspects of implementation that may be confusing to investigators. We recommend the following processes be clarified prior to the effective date of the final policy:

1. *Determination of whether a project meets the NIH definition of clinical trial:* The NIH FAQ, FDAAA- Further Resources for NIH Grantees (http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#832) indicates that 'investigators and institutional officials ... are encouraged to work together to determine whether or not an NIH grant is supporting an applicable clinical trial, and whether or not that trial must be registered under FDAAA. This determination is communicated to the NIH in the grantee's certification of compliance with FDAAA.' If the investigator/Institution makes a decision as to whether research qualifies as a clinical trial under this policy and NIH disagrees, how will this be communicated to the investigator/institution? Through the Notice of Grant Award? Who has final authority to make the determination regarding whether a study meets clinical trial definition? The NIH or the grantee institution?
2. *Effective Date:* The draft indicates the policy is effective for competing grant applications and, contract proposals submitted, received, or initiated after the effective date. We recommend that NIH provide further clarity regarding the applicability of the policy, if any, to noncompeting NIH supported clinical trials as of the effective date. Specifically, please clarify if results reporting will be required for
 - a. A clinical trial in which the primary completion date is reached shortly *after* the effective date;
 - b. A clinical trial in which the primary completion date is reached shortly *before* the effective date;
3. *Direct charging FDAAA compliance costs to NIH grants:* The NIH FAQ, FDAAA- Further Resources for NIH Grantees (http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#836) states that the cost of FDAAA compliance will generally be allowable as a direct charge to NIH supported grants. We recommend that the NIH provide examples of allowable costs) for registration and results reporting efforts, e.g., whether biostatistician support and data entry costs are allowable and approximate expectations for registration and results data entry.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification.

Sincerely,

A handwritten signature in blue ink, appearing to read 'H. Orf', with a long, sweeping flourish extending to the right.

Hanv W. Orf, PhD
Senior Vice President for Research
Massachusetts General Hospital

Co

From: [Richard Price](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: EAHP response to HHS/NIH consultation
Date: Monday, March 23, 2015 10:11:59 AM
Attachments: [4BBFE8C1-A4F2-45C7-B803-109154B894E9\[25\].png](#)
[47196879-EF4B-485B-BE42-4922AA89A170\[25\].png](#)
[91315BCD-FEC4-4B1D-ABB8-E557599A1823\[25\].png](#)
[23B4AF7F-DE4F-4635-BF17-2EC8876236E0\[25\].png](#)
[EAHPresponseNIHCTconsultation.pdf](#)
Importance: High

Dear Sir/Madam,

Please find attached the response of the European Association of Hospital Pharmacists to the consultation by HHS/NIH on proposals to enhance transparency of clinical trial results.

With the matter being of such high interest to the international research and health community, we value the opportunity provided to present opinion.

I would be grateful for email confirmation of successful receipt of our response.

Kind regards,

Richard Price

Richard Price

Policy and Advocacy Officer

European Association of Hospital Pharmacists (EAHP)

Rue Abbé Cuypers, 3 B - 1040 Brussels, Belgium

Tel: +32 (0) 2/741.68.35 | Fax: +32 (0) 2/734.79.10

e-mail: richard.price@eahp.eu

www.eahp.eu

EU Transparency Register ID Number: [82950919755-02](#)

Attend the 20th EAHP Congress – Hamburg, Germany 25-27 March 2015

Congress Focus: "The hospital pharmacist's agenda – patient safety first"



making the difference in medication

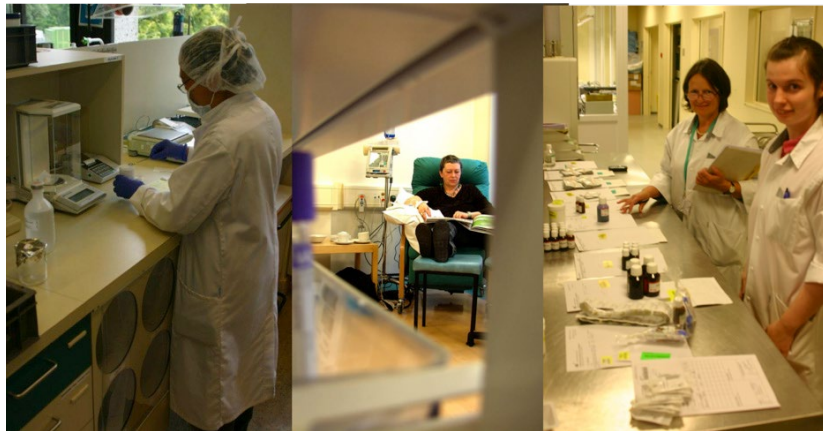


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European Association of Hospital Pharmacists (EAHP)

Consultation Response to the HHS/NIH proposals to enhance transparency of Clinical trial results



March 2015

Welcoming international improvement of clinical trial registration and result transparency

The European Association of Hospital Pharmacists (EAHP) is an association of national organisations representing hospital pharmacists at European and international levels. With national member associations in 34 European countries, EAHP represents approximately 21,000 hospital pharmacists.

Since June 2013 EAHP has been an active signatory organisation and supporter of the Alltrials campaign to ensure all past and present clinical trials are registered and their full methods and summary results reported. With this in mind, we have been encouraged to respond to the Department of Health and Human Services (HSS) and National Institutes of Health (NIH) consultations relating to trial reporting. With the matter of clinical trial transparency being of such high interest to the international research and health community, we value the opportunity provided to present opinion. We are therefore pleased to read of the positive proposals for improved transparency that are suggested and are motivated to signal to the proposal authors the support that exists for the measures at a global level. We congratulate the agencies not only on its open consultation and welcome for international responses, as well as the proactive publication of responses as received.

Comments on the proposed expansion of trial registration and reporting requirements

The proposal to mandate a responsible party to submit summary results information to ClinicalTrials.gov for any applicable clinical trial that is required to be registered, regardless of whether the drugs, biological products, or devices under study have been approved, licensed, or cleared for marketing by the FDA, appears a notable advance on current requirements, and in keeping with developments taking place in Europe following the 2014 EU clinical trials regulation¹. Equally, new requirements for results information to be submitted not later than 1 year after the completion of the clinical trial is in keeping with requirements set out in the 2014 EU regulations. EAHP therefore welcomes these proposals and is encouraged by an apparent converging of transparency requirements.

Comments on making registration and reporting of a trial a condition of funding

NIH is to be applauded for responding to the clear evidence of problems in terms of unreported trial results. EAHP hopes other funding organisations across the globe can follow this positive lead. It is also welcomed that the policy includes Phase 1 trials small feasibility

¹ http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

studies of devices, and clinical trials of behavioral, surgical, and other types of health and medical interventions.

Final comments

Beyond the above, EAHP conveys a general desire that the positive developments in clinical trial databases taking place in both the USA and the European Union, where possible, be made in communication with each other. More particularly, it would aid the international research community if harmonised terminologies, and similar database functionalities and modalities, could be strived for. With the European Medicines Agency currently undertaking a major overhaul of its clinical trial database as part of the implementation activity of the 2014 EU clinical trials regulation², there appears to be a unique window of opportunity to make further progress in achieving commonalities. Whilst jurisdiction for clinical trial databases may not take place at an international level, the utilisation by researchers and interested parties of such portals surely does.

In the long term, some convergence, where sensible and practical, of trial requirements in respect of reporting (e.g. time points at which a trial should be registered, fields of information), may assist in terms of facilitating the conduct of, access to information about, and understanding of, international trials. However it is understood this goes beyond the immediate remit of the Department of Health and Human Services (HSS) and National Institutes of Health (NIH) consultations.

Lastly, we encourage communication to take place between responsible agencies in the USA and European Union on the scope for better linkages between the clinical trial register in the USA and the EU's EudraCT, for example, common identifications for studies registered in both the USA and Europe.

Should our Association be able to provide further information or supporting documentation for the points raised above, that could be helpful in future stages of NIH/HHS policy development in relation to clinical trial result transparency, we would be delighted to assist in such a way.

² http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

From: [Jacquelyn Bendall](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comment letter
Date: Monday, March 23, 2015 12:44:17 PM
Attachments: [NIH Draft PolicyCTfinjb.pdf](#)

To Whom this May Concern,

Please find the attached comment letter pertaining to the Draft NIH Policy on Dissemination of NIH Funded Clinical Trial Information. We appreciate the opportunity to comment.

Sincerely,

Jackie Bendall
Council on Governmental Relations
1200 New York Avenue NW
Suite 750
Washington DC 20005
(202) 289-6655 ext.117
<http://www.cogr.edu/>

COGR

an organization of research universities

COUNCIL ON GOVERNMENTAL RELATIONS1200 New York Avenue, N.W., Suite 750, Washington, D.C. 20005
(202) 289-6655/(202) 289-6698 (FAX)**BOARD OF DIRECTORS**SUSAN CAMBER, Chair
University of Washington

March 23, 2015

SARA BIBLE
Stanford UniversityOffice of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892LOIS BRAKO
University of Michiganclinicaltrials.disseminationpolicy@mail.nih.govPAMELA CAUDILL
Harvard UniversityKELVIN DROEGEMEIER
University of Oklahoma

Subject: NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

JOSEPH GINDHART
Washington University in St. Louis

To Whom this May Concern:

CYNTHIA HOPE
University of Alabama

The Council on Governmental Relations (COGR) is an association of 190 research universities and their affiliated academic medical centers and research institutes. COGR concerns itself with the influence of federal regulations, policies, and practices on the performance of research conducted at its member institutions. We and our members appreciate the opportunity to comment on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

MICHAEL LUDWIG
University of ChicagoJAMES LUTHER
Duke University

We support the interest of the NIH to advance the translation of research results into knowledge, products, and procedures that improve human health. We recognize that transparency of information concerning clinical trials is critical to researchers, physicians, patients, and the general public ("stakeholders") in order to reduce bias, avoid duplication, and expedite scientific discoveries. However, we are concerned that the NPRM as currently written and NIH's proposed plan to apply this policy to all NIH funded clinical studies regardless of study phase, type of intervention, or whether they are subject to the FDA regulations will not only increase burden for our member institutions, but will be very difficult for them to maintain compliance within the timeframes cited. We believe that in order to achieve successful outcomes to proposed policy and any resultant regulation, consensus and harmonization of data must be obtained among all stakeholder groups including federal agencies prior to any further proposed changes and implementation. Further, we see no evidence that the proposed NIH policy as currently drafted supports the mission to advance the translation of research results into knowledge, products, and procedures that improve human health for reasons cited below.

LYNN MC GINLEY
University of Maryland, BaltimoreALEXANDRA MC KEOWN
The Johns Hopkins UniversityKIM MORELAND
University of WisconsinKERRY PELUSO
Emory UniversityCORDELL OVERBY
University of DelawareSUZANNE RIVERA
Case Western Reserve UniversityPATRICK SCHLESINGER
University of California, BerkeleyJAMES TRACY
University of KentuckyPAMELA WEBB
University of MinnesotaDAVID WINWOOD
Louisiana State UniversityKEVIN WOZNAK
Georgia Institute of Technology

Unique to academia, unlike other entities, researchers wear many hats often balancing their administration duties, with those of teaching, research, consulting, clinical practice, and service to their communities, all of which bear significance and importance. If the additional reporting and compliance requirements (and subsequent short turnaround deadlines) will be applicable to all NIH clinical studies, there will be a stark increased need for additional administrative support and other resources to comply. As you are aware, Institutions of Higher Education continue to be subject to an administrative cost cap of 26% making this another costly unfunded mandate IHE's must address. The additional administrative burden and lack of resources to add administrative support for our investigators creates an environment that opposes the advancement of public health and detracts from advances in clinical research. Further indirect implications include the encroachment on already pressed time spent in writing proposals for new and innovated research and mentorship activities.

ANTHONY DE CRAPPEO
President

While the cost impact to enter all clinical studies into clinical trials.gov is minimal and takes one quarter of the time it takes for result reporting, monitoring and quality assurance, we believe that the costs of implementing the NIH policy (including the NPRM) far outweigh the benefits when the vast majority of researchers already register their studies due to the desire to publish in journals. The NPRM outlines costs tied to the regulation, these costs are not recognized in the NIH Draft Policy: i.e. additional National Library of Medicine (NLM) staff required to process 600 trials per year, 24,000 hours per year to input results, thousands of hours of institutional time to reconfigure/redesign systems to manage, support, and monitor compliance with the policy, and additional NLM and institutional time to account for other special circumstances including but not limited to behavioral trials for which the systems were not initially designed.

While we agree that journal publication is not always possible and that many clinical trials are not being published or published in a timely manner, we ask that you exclude from reporting small pilot studies. The small pilot studies designed to examine the feasibility of an approach that is intended to be used in a larger scale study, might confuse rather than heighten public understanding (the reason for issuance of the NPRM and NIH Draft Policy), thereby diverting resources that could more usefully be devoted to larger studies. Similarly, studies with multiple screen failures or enrollment problems add little to results reporting for the patient population, but may add value for physicians or researchers, again, adding merit to COGR's stance that a "one-size-fits-all" model to data sharing will be less efficient for promoting public understanding. Given that contact information is already available in clinicaltrials.gov for interested parties wanting more information for these types of situations, we ask that you re-consider results reporting for certain studies and the costs and burden that would be eliminated for institutions should these trials be eliminated.

The Draft NIH Policy (and the NPRM) does not recognize the current onerous website interface, and the resources it will require of our member institutions to properly train current and new staff, and to communicate, manage and monitor the abundance of data being requested within the timelines cited. We ask that you consider this in context with the increased applicability of studies and devices and the burden it will add to an already onerous system interface difficult to navigate if improvements aren't made *before* implementing additional requirements.

We implore you to partner with patient stakeholders and the broader community alike in determining a thoughtful and carefully planned approach of data sharing and storage that can be more easily understood and broadly shared. We ask that DHHS work with the stakeholder community to develop a data sharing plan(s) specific to generating successful outcomes mutually beneficial to satisfy all stakeholder groups and to recognize the risks placed on institutions and faculty as a result of accepting federal funds, that subject them to scrutiny for non-compliance including breaches of patient records.

In closing, we appreciate the opportunity to provide our comments and we support the need to provide patients with more data and transparency necessary to inform good decisions. We advocate for additional analysis and to consider all stakeholders input before implementing arduous regulations that add extensive burden to institutions. We ask that you harmonize with other agencies and acknowledge efforts currently underway to promote public awareness ensuring efforts aren't duplicated unnecessarily.

Thank you for your willingness to review COGR's recommendations. Please contact me or Jackie Bendall at (202) 289-6655. We look forward to working with you to address these important issues.

Sincerely,



Anthony P. DeCrappeo
President

From: [Ian Bushfield](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: AllTrials Comments on Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information Notice Number: NOT-OD-15-019
Date: Monday, March 23, 2015 1:03:06 PM
Attachments: [AllTrials 2015 Mar Response to NIH Policy Final.pdf](#)

To the Office of Clinical Research and Bioethics Policy, Office of Science Policy, NIH

Please accept the attached comments regarding the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information Notice Number: NOT-OD-15-019.

Best wishes

Ian

--

Ian Bushfield
Campaigns Support Officer

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AllTrials: [Web](#) | [Twitter](#) | [Facebook](#)

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Registered Charity No. 1146170, Company No. 6771027.

AllTrials Comments on Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

Notice Number: NOT-OD-15-019

To: Office of Clinical Research and Bioethics Policy, Office of Science Policy, NIH

Email: clinicaltrials.disseminationpolicy@mail.nih.gov

23rd March 2015

The AllTrials campaign¹ strongly welcome the proposed NIH policy to make registration and reporting of results a condition of receiving an NIH grant for any clinical trial and to hold trial sponsors to the same timelines laid out by FDA Amendment Act 2007. The new policy will help ensure that the results of clinical trials will be available and that the efforts of the patients in those trials will be counted.

An independent audit published in the *New England Journal of Medicine* in 2015 found only 8.1% of trials funded by NIH reported results within one year of trial completion². NIH is in a strong position to shift the cultural norms around the dangerous practice of withholding trial results, and can lead the way for other academic and government funders.

NIH should require, as part of a condition of grant funding, that researchers have registered and reported results of their previous trials. The vast majority of medicines we use every day were approved by regulators a decade or more ago and so were tested in clinical trials in the decades before that. The best available evidence^{3,4} is that around half of all clinical trials have not reported results. Doctors, patients and funders of health services cannot make informed decisions about which treatment is best, if half of all the trial results on that treatment are withheld. NIH has the opportunity to institute a policy to make the results of many of these past trials available and we urge you to take it.

Industry and academic trial sponsors have shown that it is possible to register and report the results of past trials. After wide consultation with its stakeholders, the UK Health Research Authority (HRA) made registration of a clinical trial a condition of ethics approval in September 2013. And from 1st April 2015, the HRA will require sponsors to declare that all their trials started since September 2013 and all trials currently in active recruitment have been registered. Pharmaceutical companies LEO Pharma is making results available for trials it has run since 1990⁵, Bristol-Myers Squibb is making results available for trials it has run since 2008⁶ and GlaxoSmithKline is making results available for its trials since 2000⁷.

Signed by

Síle Lane

Director of Campaigns

Sense About Science

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slane@senseaboutscience.org

¹ The AllTrials campaign was launched in January 2013 and calls for all past and present clinical trials to be registered and their results reported. It is an initiative of Bad Science, BMJ, Centre for Evidence-based Medicine, Cochrane Collaboration, James Lind Initiative, PLOS and Sense About Science and is being led in the US by Sense About Science US!, Dartmouth's Geisel School of Medicine and the Dartmouth Institute for Health Policy & Clinical Practice. Since then, the AllTrials petition has been signed by over 83,000 people and 545 organisations. Many supporters of the AllTrials campaign will also be submitting their own responses.

² ML Anderson, K Chiswell, ED Peterson, A Tasneem, J Topping, and RM Califf, Compliance with Results Reporting at ClinicalTrials.gov. *N Engl J Med* 2015; 372:1031-1039 DOI: <http://dx.doi.org/10.1056/NEJMsa1409364> (Published 12 March 2015)

³ F Song, S Parekh, L Hooper, YK Loke, J Ryder, AJ Sutton, C Hing, CS Kwok, C Pang, I Harvey. Dissemination and publication of research findings: an updated review of related biases. *Health Technology Assessment* 2010; Vol. 14: No. 8 http://www.journalslibrary.nihr.ac.uk/data/assets/pdf_file/0005/64751/FullReport-hta14080.pdf.

⁴ Schmucker C, Schell LK, Portalupi S, Oeller P, Cabrera L, et al. (2014) Extent of Non-Publication in Cohorts of Studies Approved by Research Ethics Committees or Included in Trial Registries. *PLoS ONE* 9(12): e114023. doi: 10.1371/journal.pone.0114023 <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114023>

⁵ <http://www.leo-pharma.com/Home/Research-and-Development/Clinical-trial-disclosure/LEO-Pharmas-position-on-transparency.aspx>

⁶ http://www.bms.com/clinical_trials/pages/disclosure.aspx

⁷ <http://www.gsk.com/en-gb/our-stories/how-we-do-randd/data-transparency/>

From: [Riley, Susan F](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [White, Sarah Alicia](#)
Subject: McLean Hospital Response to NIH policy 3.19.15
Date: Monday, March 23, 2015 1:14:56 PM
Attachments: [McLean response to NOT-OD-15-100001.pdf](#)

To Whom it May Concern –

Thank you for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-019)*. Attached is Dr. Scott Rauch's response on behalf of McLean Hospital.

Thank you,

Sue Riley for Scott L. Rauch, MD

*Sue Riley
Executive Assistant to Scott L. Rauch, M.D.
President and Psychiatrist in Chief
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Scott L.-Rauch, MD

President and Psychiatrist-in-Chief
Rose-Marie and Eijk van Otterloo Chair of Psychiatry

Professor of Psychiatry
Chair, Partners Psychiatry and Mental Health

March 19, 2015

RE: NOT-OD-15-019: NIH Draft Policy on Clinical Trials Registration and Results Reporting

Thank you very much for providing the opportunity to comment on the NIH draft policy, *Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019)*. I am writing on behalf of McLean Hospital, an affiliate of the Massachusetts General Hospital and a member of the Partners HealthCare System. A major teaching facility of the Harvard Medical School, McLean maintains the largest program of research in neuroscience and psychiatry of any private psychiatric hospital in the U.S. In FY 14, McLean received approximately \$28 million in research funding from the NIH. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to McLean's research enterprise.

While we support the NIH's expectations and efforts to make research and results information publicly available, we are concerned that the proposed policy without clarification and revision would impose a significant administrative burden on investigators and institutions and lead to confusion over interpretation of requirements. Thus, based on our experience administering a large and diverse clinical trials research program and meeting current clinical trials registration and results reporting requirements, we respectfully offer recommendations we believe would assist the NIH in developing a clear and coherent policy.

NIH Definition of clinical trial and the effect on registration and reporting requirements

We acknowledge NIH's new definition of clinical trial to determine whether an NIH-funded clinical trial requires registration and results reporting. We appreciate that NIH has elaborated on certain terms within the definition (e.g. 'prospectively assigned', 'intervention') and published FAQs and case studies. Of note, we find the case studies particularly helpful and would welcome publication of additional case studies over time.

However, it is important to recognize that when the NIH policy and the simultaneously issued FDAAA NPRM become effective, investigators conducting PI-initiated research will need to navigate four different clinical trial definitions and registration criteria: the FDAAA definition of Applicable Clinical Trial, the NIH definition of clinical trial, the ICMJE definition of clinical trial, and the CMS definition of qualifying clinical trial. These definitions of clinical trial each differ or appear to differ from one another, in some cases in subtle ways; the associated timelines for registration and overall responsibilities (results reporting, updating the record) differ across some (but not all) of these sources of rules. In our experience, investigators are frequently

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1

confused by these various requirements and a good deal of effort and resources are required to assist them in understanding their responsibilities.

In order to support institutions and investigators in understanding and reconciling the various definitions and requirements, we strongly recommend that the NIH collaborate with FDA, ICMJE and CMS to harmonize definitions to reduce or eliminate differences. If this is not possible, we recommend a joint effort to publish guidance comparing and contrasting all requirements for clinical trials registration and results reporting. Differences in definitions should be explicitly articulated and highlighted with case studies.

Clarity with regards to privately funded studies using NIH Infrastructure

The Scope and Applicability section of the proposed NIH policy asserts that the policy '... applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the FDAAA registration and results submission requirements set forth in Section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)).'

We suggest clarification regarding privately funded studies using NIH infrastructure. We note that National Cancer Institute Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials (Notice Number: NOT-CA-15-001, release date 1/28/15) defines *NCI-Supported Clinical Trials* as follows: '...all clinical trials financially supported - whether in whole or in part - by the NCI. Clinical trials that are wholly funded by private entities (and in which the data from the clinical trial belong to the private funder) are not considered to be NCI-supported even if such studies are conducted at the NCI-designated Cancer Centers and benefit from the Cancer Center infrastructure.'

The clarification that privately funded trials using NCI supported infrastructure are not covered as part of the NCI policy is a significant detail that helps academic centers understand the scope of the policy. Clinical and Translational Science Awards (CTSA) set up infrastructure at academic institutions similar to the NCI-designated Cancer Centers. We request the Scope and Applicability section of the proposed NIH policy insert similar language which provides helpful clarity regarding privately funded studies using CTSA infrastructure.

Required results reporting for behavioral clinical trials

We appreciate that the ClinicalTrials.gov database has undergone many revisions to accommodate different types of research including behavioral and observational research. The NIH proposed policy to require results reporting of behavioral clinical trials will now include investigators who have no experience with the results database. We note that ClinicalTrials.gov has examples of studies for results data entry (parallel study design, cross-over study design, etc). These examples have been very helpful to the academic research community. We recommend that NIH, in collaboration with ClinicalTrials.gov, publish additional examples specific to behavioral study design.


Compliance with policy

The NIH draft policy does not provide specific information on certain key aspects of implementation that may be confusing to investigators. We recommend the following processes be clarified prior to the effective date of the final policy:

1. *Determination of whether a project meets the NIH definition of clinical trial:* The NIH FAQ, FDAAA- Further Resources for NIH Grantees (http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#832) indicates that 'investigators and institutional officials ... are encouraged to work together to determine whether or not an NIH grant is supporting an applicable clinical trial, and whether or not that trial must be registered under FDAAA. This determination is communicated to the NIH in the grantee's certification of compliance with FDAAA.' If the investigator/Institution makes a decision as to whether research qualifies as a clinical trial under this policy and NIH disagrees, how will this be communicated to the investigator/institution? Through the Notice of Grant Award? Who has final authority to make the determination regarding whether a study meets clinical trial definition? The NIH or the grantee institution?
2. *Effective Date:* The draft indicates the policy is effective for competing grant applications and, contract proposals submitted, received, or initiated after the effective date. We recommend that NIH provide further clarity regarding the applicability of the policy, if any, to noncompeting NIH supported clinical trials as of the effective date. Specifically, please clarify if results reporting will be required for
 - a. A clinical trial in which the primary completion date is reached shortly *after* the effective date;
 - b. A clinical trial in which the primary completion date is reached shortly *before* the effective date;
3. *Direct charging FDAAA compliance costs to NIH grants:* The NIH FAQ, FDAAA- Further Resources for NIH Grantees (http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#836) states that the cost of FDAAA compliance will generally be allowable as a direct charge to NIH supported grants. We recommend that the NIH provide examples of allowable costs for registration and results reporting efforts, e.g., whether biostatistician support and data entry costs are allowable and approximate expectations for registration and results data entry.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification.

Sincerely,



Scott L. Rauch, M.D.

From: [Stephanie Mohl](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Comment Letter from American Heart Association
Date: Monday, March 23, 2015 3:31:45 PM
Attachments: [image003.png](#)
[image004.png](#)
[image005.png](#)
[image006.png](#)
[image007.png](#)
[image008.png](#)
[image009.png](#)
[image010.png](#)
[2015-03-23 NIH Clinical Trials Reporting Comments final.pdf](#)

Good afternoon. Please find attached a comment letter from the American Heart Association in response to the NIH's draft policy for registration and reporting of results for NIH-funded clinical trials. The same letter was also submitted via Regulations.gov to the docket on NIH's proposed rule on Clinical Trials Registration and Results Submission. Thank you for your consideration of our comments.

Warm regards,
Stephanie

Stephanie Mohl
Senior Government Relations Advisor
Department of Advocacy

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Lynne M. Darrouzet, Esq.

March 23, 2015

Francis S. Collins, MD, PhD
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

RE: Clinical Trials Registration and Results Submission Proposed Rule (RIN 0925-AA52 and Docket Number NIH-2011-0003) and Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-15-019)

Dear Dr. Collins:

We are pleased to provide these comments to the National Institutes of Health (NIH) in response to its notice of proposed rulemaking for registering and submitting summary results of certain clinical trials to ClinicalTrials.gov and its draft policy for extending similar registration and reporting requirements to all clinical trials funded by the NIH. The American Heart Association applauds NIH for proposing greater transparency of clinical trial registration and summary result information. Such information is critically important to the 85.6 million Americans with heart disease, stroke, or other forms of cardiovascular disease (CVD), to clinicians, to researchers, and to our nation as a whole.

The Association has long recognized the value of clinical trials in advancing medical science and treating and curing disease. Since 1949, the Association has invested more than \$3.7 billion in research to increase our knowledge about cardiovascular diseases and stroke and currently funds more than 2,000 scientists around the United States. We affirm the pivotal importance of clinical trials as a key basis for the development of evidence-based clinical practice guidelines in support of our mission. In order to provide clinicians with best practice recommendations that will help them improve outcomes at point-of-care, there is an urgent need to conduct research that addresses current gaps. To this end, we agree that researchers and trial sponsors have an obligation to share information about and results of clinical trials in a swift and transparent manner. We are generally very supportive of the NIH's draft policy and proposed rule and offer the following specific comments about these proposals.

Draft NIH Policy

The NIH draft notice would require all NIH-funded clinical trials to submit registration and results information to ClinicalTrials.gov, regardless of study phase, type of intervention, or whether they are subject to the registration and reporting requirements under the Food and Drug Administration Amendments Act of 2007 (FDAAA). As NIH noted in the draft policy, a 2012 study found that the results of fewer than half of NIH-funded clinical trials had been published in a peer-reviewed biomedical journal within 30 months of trial completion. The selective publication of trial results, and particularly the suppression of negative results, can be harmful to patients in a number of ways: It can lead to inaccurate or inappropriate conclusions about the efficacy of a particular therapy, result in duplication of unsafe or unsuccessful trials, and slow progress in the understanding of disease and therapies for treatment. Such damage is particularly unacceptable and unethical when the research is being funded by taxpayers who expect and deserve that their tax dollars are being used in a manner that maximizes efficiency and the advancement of the public health. Given these compelling arguments for greater transparency, we enthusiastically support finalizing the NIH Policy as soon as possible.

NPRM Subpart A – General Provisions

The rule generally and this subpart specifically implements Title VIII of FDAAA, which requires the NIH to expand the nation's clinical trials databank, ClinicalTrials.gov, to include registration and summary result information for a wider range of research studies.

A single, comprehensive database can help to improve patient participation in clinical trials by making it easier for them to identify studies in which they may be eligible to participate. The Association believes it is particularly important to improve the representation of women, minorities, and older adults in clinical trials, given that numerous studies have found that these populations have long been underrepresented in cardiovascular clinical trials. We recognize that there are many reasons why women, minorities and older adults may not participate in clinical research, but research shows that a significant reason why is that they are not being sought out for inclusion.¹ While the impetus should be placed on trial sponsors to ensure adequate diversity in enrollment, educating the public about how they can seek out opportunities to participate in clinical trials may also help improve subgroup representation.

The Institute of Medicine, in its January 2015 consensus report, *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*,² made a number of recommendations for sponsors and investigators to share various types of clinical trial data, following timeframes recommended by the committee. More specifically, the IOM recommends that:

¹ Society for Women's Health Research and U.S. Food and Drug Administration. Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials. September 2011. Accessed online at:

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM334959.pdf>.

² Institute of Medicine (IOM). 2015. *Sharing clinical trial data: Maximizing benefits, minimizing risk*. Washington, DC: The National Academies Press.

- Registration information be publicly available before the first participant is enrolled in a trial;
- Summary-level results be publicly available within 12 months of study completion;
- For studies supporting product approval, that the “postregulatory data package” be available within 30 days of product approval or 18 months after study completion, whichever is later; and
- For products for which approval is abandoned, that the postregulatory data package be available within 18 months after abandonment.

We note that the timeframes for registration and availability of results information recommended by the IOM vary somewhat from those being proposed by the NIH. To the extent feasible, we urge NIH to conform its timeframes to those recommended by the IOM when finalizing its rule and notice.

NPRM Subpart B -- Registration

The rule generally proposes that the sponsor or principal investigator register an applicable clinical trial at ClinicalTrials.gov within 21 days of enrolling the first participant and specifies the descriptive information, recruitment information, location and contact information, and administrative information that must be provided. The rule also proposes the timeframes by which the NIH will publicly post clinical trial registration information for applicable drug (and biologic) trials and for applicable trials for approved or cleared devices and for applicable trials for devices not previously approved or cleared. We support these requirements with the following improvements.

First, in addition to the 25 data elements (including gender, age limits, and inclusion and exclusion criteria) that NIH plans to require at the time of registration, we propose that sponsors be required to submit projected target recruitment goals by gender, race and ethnicity, and age. Submitting this information would not require sponsors to revise their clinical trial designs or to collect new information during the conduct of the trial, but it would shine greater light on the need for inclusion of these subgroups and hopefully encourage sponsors to proactively and prospectively develop plans to enroll sufficient proportions of women, minorities and older adults to meet their own targets.

As NIH points out in the proposed rule, the statute allows for modification of the registration information if rationale is provided as to “why such a modification improves and does not reduce” such information. Requiring sponsors to report their target recruitment goals by subgroup would enhance, not supplant, the required recruitment and enrollment information.

In addition, NIH proposes to require sponsors to submit actual enrollment data once enrollment in the trial has closed. We encourage NIH to also require sponsors to report actual enrollment data by subgroup as a means of measuring how actual enrollment compared with the projected target recruitment goals by gender, race and ethnicity, and age.

The NIH also invites comments on how it may allow sponsors of device trials that previously have not been approved or cleared to have registration information posted publicly through ClinicalTrials.gov when the responsible party chooses. As NIH notes in the preamble, there may be a number of reasons why the sponsor may want to make registration information publicly accessible, including to assist with or expand upon patient recruitment efforts. We support allowing a responsible party to voluntarily give NIH permission to post clinical trial registration information in such an instance and encourage NIH to include such a provision in the final rule.

NPRM Subpart C – Results Submission

This section of the proposed rule lays out when and how clinical trial results must be submitted to ClinicalTrials.gov and when the NIH will post this information. Once again, we are generally supportive of NIH's efforts to ensure the broader dissemination of research results. As we noted above, making both positive and negative research findings publicly available is in the best interests of patients and the advancement of science. In addition, the information being submitted is summary level data and would not contain personally identifiable information.

In particular, we support NIH's intention to require that summary results be submitted for applicable drug and device clinical trials that are not approved, licensed, or cleared by the FDA. NIH lays out in the preamble a number of compelling reasons for requiring the submission and public availability of summary results for such products, including the need to protect patients from unknowingly participating in clinical trials that are unnecessary (because similar trials have already been conducted but not published) and the ethical obligation to human subjects to use the knowledge gained from the trial they participated in to advance medical science. In addition, we note that the European Union is already taking steps to require public disclosure of clinical trial results for drugs, regardless of the approval status of the drug. We believe the NIH has appropriately recognized and balanced concerns about commercial competitiveness by providing for delay of the results submission deadline for products that are still under development.

When submitting results information, NIH plans to require reporting of age and gender as demographic characteristics of trial participants but does not propose to require reporting of race and ethnicity data. FDA regulations and guidance do require product sponsors to report race and ethnicity information, as well as gender and age information. A 2013 FDA report, *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*, found that, while drug and biologic product sponsors were generally reporting race and ethnicity information in their applications, this information was not consistently available in device applications. Applications were credited with including this information even when the rates of participation for specific racial or ethnic subgroups were very low or even zero. We urge NIH to therefore require submission of race and ethnicity information to ClinicalTrials.gov as a means of furthering the goal of greater consistency in the reporting of subgroup data across government agencies. Improved consistency in the reporting of race and ethnicity data across trials could allow for pooling of subgroup data in order to allow for better subgroup analyses to be conducted.

The NIH also invites public comment on the provisions of FDAAA that require non-technical and technical summaries of clinical trial results to be included in

ClinicalTrials.gov “if the Secretary determines that such types of summary can be included without being misleading or promotional.” We do believe that summary trial information and results that is written in a non-technical, understandable, accurate and objective manner would be particularly helpful for patients. As a model for how to do this, NIH may want to consider the FDA’s new Drug Trials Snapshots initiative, an effort to provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs and to highlight whether there were any differences in the benefits and side effects of new drugs among sex, race and age groups.

Thank you for this opportunity to comment on the NIH’s proposed rule and draft policy to promote greater transparency and dissemination of clinical trials results. The Association looks forward to continuing to partner with NIH to further responsible sharing of clinical trial data.

Sincerely,

A handwritten signature in black ink, reading "Elliott M. Antman, MD". The signature is written in a cursive style with a large initial "E" and a stylized "A".

Elliott M. Antman, MD, FAHA
President

From: [Nuala Moore \(DC\)](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: ATS Comments on Clinical Trials NPRM
Date: Monday, March 23, 2015 3:52:14 PM
Attachments: [ATS-NIHclinicaltrialsletter3-15.pdf](#)

Dear NIH Staff:

Attached are the American Thoracic Society's comments on the clinical trials NPRM, RIN 0925-AA52 & Docket Number NIH-2011-0003. Thank you for your consideration.



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March 23, 2015

Francis Collins, M.D.
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RE: RIN 0925-AA52 & Docket Number NIH-2011-0003

Dear Dr. Collins:

The American Thoracic Society (ATS) appreciates the opportunity to comment on the national Institute of Health (NIH)'s recent NPRM proposals to enhance transparency of clinical trial results.

General Comments

The ATS welcomes the proposed changes that aim to increase the transparency of clinical trial data reporting and to improve decision making by patients and clinicians by enhancing access to up-to-date clinical trial data. This is an important and necessary step towards correcting existing problems with the current clinicaltrials.gov website.

There are, however, certain ambiguities in terminology and formulation of these proposed regulations that may continue to allow or facilitate the registration of unregulated or poorly regulated clinical trials as well as stem-cell and other medical tourism types of activities to the ClinicalTrials.gov website. This may result in public dissemination and visibility of misleading information. For example, the use of various terms in the proposed new regulations such as "certain clinical trials", "applicable clinical trials", and "specified clinical trials" to stipulate what needs to be listed in the registry is a potential source of confusion. A well-defined terminology that would unequivocally identify the type of clinical trials to which the new regulations apply would be preferable.

Further clarification of what constitutes a well-conceived and designed clinical trial would also be a helpful and welcome step for both the final rule and practices for listing trials on the ClinicalTrials.gov website.

Adverse Events Reporting

With regards to the reporting of adverse events, we recommend that the NIH revisit the attribution requirements as the goal is to identify (as best as possible) what is attributable to the therapy and not the disease. We suggest that the same major category be kept, with two subcategories to delineate between the therapies versus disease. Stratification around the 5% threshold could be considered for expected versus unexpected adverse events.

Section 11.60 of the proposed rule

The ATS notes the voluntary submission of information is allowed for certain types of non-applicable clinical trials, such as Phase I trials under the proposed rule §11.60. This may include information on trials of unapproved, unlicensed, and unregulated products (<http://www.nih.gov/news/health/nov2014/od-19.htm>). We are concerned that this provision may dilute the reliability and integrity of the information submitted. In particular, the possibility remains that unproven stem cell and cell-based therapy interventions that lack solid preclinical data may be advertised to the public and clinicians under the guise of registered Phase I trials. The potential for abusing the mechanism of voluntary submission is illustrated by the observation that of the 182,821 trials listed on ClinicalTrials.gov only 34,413 trials (18.8%) are actively recruiting patients (information current as of January 27 2015). Of those, 52% are based outside of the U.S. and most likely voluntary submissions. A possible safeguard against the listing of medical tourism-like activities is the requirement of “U.S. FDA Approval, Licensure, or Clearance Status,” or similar from Competent Authorities operating in countries to carry out clinical trials in compliance with ICH Clinical Trial for each intervention by rule §11.60. We believe that introducing a request for the name of the regulatory agencies who have already reviewed the preclinical data as part of an authorized clinical trial application and reference to peer-reviewed scientific publications may further protect patients and clinicians for promotional and deceptive information.

The proposal for inclusion of a lay (non-technical) summary of clinical trial results is a positive and welcome development as it will make understanding of complex information more accessible to the general public. By providing a tool that is patient-focused and public friendly, we believe that NIH can better inform patients, families and caregivers throughout the clinical trials process and improve recruitment in clinical trials in the U.S. through the creation of a more inclusive and transparent system. Although there are real risks of oversimplification of complex outcome measures or of inclusion of promotional and misleading material, as pointed out in the full text of the proposed rules, we strongly believe that both technical and non-technical summaries of the clinical trial results should be submitted for each trial. To ensure the veracity and integrity of these documents, stringent criteria and penalties should be established similar to the ones for noncompliance. We encourage NIH to consider developing a strategy to deter non-compliance.

Finally, the ATS recommends that the NIH establish and maintain a ClinicalTrials.gov public advisory committee consisting of researchers, industry representatives, and patient representatives. By including strong patient-focused engagement in this manner, we believe this advisory committee would ensure the long-term success of the ClinicalTrials.gov website.

The ATS thanks the committee for the opportunity to comment. If you have any questions, please Contact Nuala Moore, Associate Director of Government Relations at 202.296.9770 or Nmoore@thoracic.org.

Sincerely,

A handwritten signature in black ink, appearing to read "Tom Ferkol". The signature is written in a cursive, flowing style.

Tom Ferkol, M.D.
President
American Thoracic Society

From: [Heather Pierce](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Stephen Heinig](#)
Subject: NOT-OD-15-019: Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
Date: Monday, March 23, 2015 5:01:41 PM
Attachments: [HHS CT Registration and Results NIH Policy 03-23-2015.pdf](#)

Please see the attached comments from the Association of American Medical Colleges on the above referenced draft policy. Do not hesitate to reach out to me or to my colleague Stephen Heinig with any questions.

Heather H. Pierce, JD, MPH

Senior Director, Science Policy
Regulatory Counsel, Scientific Affairs
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March 23, 2015

NIH Regulations Officer
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6011 Executive Boulevard, Suite 601, MSC 7669
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Office of Clinical Research and Bioethics Policy
Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Docket No. NIH-2011-0003, Comments on “Clinical Trials Registration and Results Submission” 79 FR 69566-680 (Submitted at regulations.gov)

Re: Notice NOT-OD-15-019, Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (Submitted via email to: clinicaltrials.disseminationpolicy@mail.nih.gov)

The Association of American Medical Colleges (AAMC) is a not-for-profit association representing all 141 accredited U.S. medical schools, nearly 400 major teaching hospitals and health systems, and 90 academic and scientific societies. Through its member institutions and organizations, the AAMC represents 128,000 faculty members, 83,000 medical students, 110,000 resident physicians, and thousands of graduate students and post-doctoral trainees. Our member organizations and their faculty include the nation’s preeminent clinical researchers. The AAMC appreciates the opportunity to submit comments on the above referenced Notice of Proposed Rulemaking, *Clinical Trials Registration and Results Submission* issued by the Department of Health and Human Services (HHS) and the related policy issued by the National Institutes of Health (NIH). Specific comments on both the proposed rule and the NIH draft policy are included in this letter.

The AAMC has strongly supported clinical trials registration and sharing of information from clinical studies. We were a leading proponent advancing the National Library of Medicine’s ClinicalTrials.gov website as the uniform, comprehensive national registry for clinical trials in 2004. In 2007, following a meeting of the AAMC’s Advisory Panel on Research and authorities on issues pertaining to the database, including the ClinicalTrials.gov director, and a journal editor and member of the International Committee of Medical Journal Editors, the AAMC issued a statement urging medical schools and teaching hospitals that conduct interventional studies on human research subjects to amend their own institutional policies to provide for trials registration. The intent of the Association’s statement, which preceded the 2007 Food and Drug Administration Amendments Act (FDAAA), was not only to facilitate compliance with the then-pending legislation, but to reaffirm publicly the view of our member institutions and clinical

investigators that research on human subjects “is ethically justified only to promote generalizable knowledge.”¹

The AAMC is supportive of the proposed rule extending the FDAAA’s requirements to all applicable trials, not only those for which the drug or device has received FDA approval. The AAMC also supports the NIH’s proposed parallel policy to extend requirements to all clinical trials meeting specified criteria funded by the agency.

Implementing both the final rule and the parallel policy should be undertaken with care to ensure the success of the agency’s goals. We encourage the NIH to carefully consider the following, each of which is further discussed below: limitations or difficulty in using the existing ClinicalTrials.gov database; the extent of effort required to submit additional data in comparison with the perceived marginal benefit to patients and the research community; the alignment of incentives and obligations for faculty researchers, particularly with posting negative results; and ensuring that the public-facing interface is both usable and clear in its utility and limitations.

A. Structure and format of the national registry

A key obstacle for posting trial results has been the lack of an effective format in the registration database that would facilitate efforts by other researchers to query and build on those results, especially across many trials, and to maximize the return even on negative results from the contributing investigators and their research. Developing such a format is challenging, and requires striking a balance to include sufficient structure for posting data in a way that enables research, while not imposing an overly complicated structure. The current ClinicalTrials.gov database lacks a structure that renders the reporting of clinical trials results usable to many clinical investigators who wish to build on the reporting and results of their peers. However, the proposed rule may actually go to the other extreme, establishing an overly complicated, “one-size-fits-all” structure.

Institutional users of the current ClinicalTrials.gov system report that limitations of the software infrastructure pose significant barriers to its effective and efficient use. For example, the inability to sort or filter the information or to create reports across one institutional account has been noted by more than one institution.

The AAMC recommends convening pilot projects with researchers and other institutional representatives to evaluate the new system for results posting, and identify the optimal, streamlined format for reporting results and facilitating queries of the data. There may be several models developed which could facilitate revisions to ClinicalTrials.gov.

¹ AAMC statement on clinical trials registration, Dec. 2007.

The success of ClinicalTrials.gov depends not only on the successful entering of data, but on a system that provides patients, research subjects, the public, and health care providers or investigators meaningful, contextual information about its contents. It is only by engaging both the likely and unlikely public users of ClinicalTrials.gov that the NIH will be able to create an improved national database. **The NIH, perhaps through the NLM’s outreach efforts, should make a concerted effort to engage patients and the public in the development of a user-friendly and useful public-facing database.**

The inclusion of many additional clinical trials as a result of the NIH draft policy, including Phase I, small volume trials, and behavioral studies, could significantly impact the strain on and complexity of the resulting database. This extent of the additional burden that this policy will impose on investigators and institutions will be driven in large part by the ease of use for the system. Before NIH implements its draft policy to require all NIH-funded trials to follow the requirements of the final rule related to ClinicalTrials.gov, the AAMC strongly urges the agency to ensure that the necessary infrastructure, interface, and context is fully in place. This may mean that a delayed or staggered implementation for certain trials would be in the best interests of the agency, the investigators, and the public. **The AAMC encourages the NIH to get additional input and user testing from both investigators and patients as this implementation begins.**

B. Addressing compliance burdens

The National Science Board, the White House Office of Science and Technology Policy, the Federal Demonstration Partnership, and previous federal initiatives have uniformly expressed profound concern for the aggregate level of effort that investigators expend in complying with requirements related to federally funded research, and how this burden affects research productivity and effectiveness.

A National Research Council committee is now looking at these concerns at the direction of Congress and the NIH, and is charged to help address this situation. Recommendations may include further harmonizing and standardizing requirements across agencies, and clarifying requirements to assist institutions’ counsel in precisely responding to obligations. The AAMC has strongly encouraged both federal agencies and the research community to evaluate the effectiveness with which various policies and regulations advance their stated objectives, and consider other and more flexible approaches for achieving these ends.²

The current proposed rule, the AAMC believes, is a case in point. The notice creates definitions that are not specified in the relevant sections of the FDAAA and that differ from those commonly used by IRBs. Many of the timeframes proposed are similarly inconsistent with other reporting requirements, and would be onerous and burdensome for compliance, without

² AAMC testimony to National Research Council, Feb. 13, 2015.

specifying how the particular requirement, as opposed to more flexible requirements, advances the interests of transparency or enabling follow-on research. There is little guidance to explain the rationale for the definitions or context.

The AAMC recommends that the demonstration project or pilot described above also consider whether the definitions and timelines should be modified in implementing the proposed regulation, specifically applying NRC recommendations on administrative burden and the IOM’s recommendations on clinical trial data sharing. A part of this effort should be for HHS and the NIH to specify the intended outcomes of the rule, how the promulgated requirements would meet those outcomes, and appropriate metrics for evaluating success.

To respond to the flexibility required when reporting results from a wide range of clinical trials, the AAMC further recommends that the final rule minimize the required fields and data. However, the NIH should work to develop ClinicalTrials.gov to accommodate a large number of elective fields and formats so that information critical or more relevant to specific trials or types of trials can be readily accommodated. The NIH should work with both investigators and the public through an iterative process to improve the quality and usability of the data.

Specific Recommendations to the Notice of Proposed Rulemaking:

1. The proposed number of updates that must be entered into ClinicalTrials.gov within 15 or 30 days of a change provides a standard that will be difficult to implement and will make full compliance with the regulations a struggle for most institutions. When possible, the timeframe in which changes must be reported should align with the requirements for the IRB review of changes in research with human subjects. These requirements are in place and well understood in academic institutions.
2. Definitions that differ from the same or similar terms in other regulations may lead to confusion or the need to create duplicate or revised processes for ensuring compliance with this regulation. Examples that are of most concern to AAMC member institutions are the proposed definitions for:
 - a. “adverse event,” which does not align with the FDA regulations;
 - b. “clinical trial,” which is very similar to the revised definition issued by the NIH but uses slightly different wording;
 - c. “completion date,” which seems to correspond with the current term “primary completion date” in the current system and may be confusing;
 - d. “intervention,” which includes the phrase “biomedical or other health related outcomes” but does not explain how to identify such a outcomes; and

- e. “study start date,” which is proposed to be the date when the study is open for enrollment or the first subject is enrolled, but is considered by many institutions to be the date of IRB approval and may lead to inconsistent internal records.
3. The AAMC agrees with previous comments that additional documents not currently specified in Section 402(j) of the Public Health Services Act should not be required through this rulemaking process. Requiring the posting of documents such as clinical trial protocols, informed consent documents, or lay summaries of the results could lead to the unintended consequences of causing these documents to be heavily redacted or drafted with the expectation that they would become public, therefore excluding detail that might be confusing to a lay audience but essential to investigators or IRBs.

C. Aligning incentives and outcomes

The optimal path to promoting a comprehensive national clinical trial registry with reported results and other pertinent information is to align incentives among researchers, research organizations, and funding agencies, rather than impose a rigid framework that may result only in *pro forma* compliance. **In addition to the steps noted above, the NIH should: encourage investigators to post negative results and facilitate this submission; facilitate and reward wide sharing of data and information; and recognize investigators and institutions who credit peers who have provided such data.**

The AAMC urges the NIH to use this opportunity to create an environment that supports effective, evidence-based regulation. The AAMC sees the current HHS proposed rule and the parallel NIH policy as part of the continuing effort to strengthen clinical trials by promoting transparency, trust, and usefulness of knowledge from human subjects research. The rule is also consistent with broader efforts to promote data sharing across medicine and science, as underscored by the Institute of Medicine’s recent report on clinical trial data sharing.³

The AAMC is again grateful for this opportunity to comment on the proposals specified in the NPRM. Please feel free to contact me, or my colleagues Heather Pierce, J.D., M.P.H. (hpierce@aamc.org) and Stephen Heinig (sheinig@aamc.org) with questions about these comments.

Sincerely,



Ann C. Borham, Ph.D.
Chief Scientific Officer

³ Institute of Medicine (IOM). *Sharing clinical trial data: Maximizing benefits, minimizing risks*. Washington, DC: The National Academies Press, 2015.

From: [Wallace, Marsha C](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Hodgson, Matthew](#)
Subject: Comments regarding NIH draft policy: Dissemination of NIH-Funded Clinical Trial Information; Notice Number: NOT-OD-15-019
Date: Monday, March 23, 2015 5:12:44 PM
Attachments: [Comments on NIH policy final032315.pdf](#)

Greetings,

RE: Draft NIH Policy: Dissemination of NIH-Funded Clinical Trial Information; Notice Number: NOT-OD-15-019

Attached, please find a copy of our comments in response to the proposed draft NIH policy noted above. Please feel free to contact our office if you have further questions or concerns.

Sincerely,

-M

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March 23, 2015

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Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

In reference to docket number: **NIH-2011-0003-0003**

Comments on Draft NIH Policy: Dissemination of NIH-Funded Clinical Trial Information

Notice Number: NOT-OD-15-019

The Children's Hospital of Philadelphia would like to thank you of the opportunity to comment on the National Institutes of Health (NIH) proposed draft policy on "Dissemination of NIH-Funded Clinical Trial Information."

As a specialty, academic center dedicated to being a world leader in advancing the healthcare of children, the Children's Hospital of Philadelphia is committed to integrating and providing excellent healthcare, through quality professional education and innovative research.

We understand the importance of, and agree with, the necessity for organizations to be transparent and provide public access of clinical trial results of NIH funded research. Enhancing transparency through disclosure and disseminating clinical trial information, contributes to generalizable, scientific knowledge. Disseminating information supports public access and allows clinicians to be informed and contribute to future research by improving study design and preventing duplication of research effort. Dissemination of information is also important to assist clinicians and potential research participants with making informed decisions about available or alternate treatment(s) as well as promote best practices for improving public health.

We would like to provide the following comments and suggestions for your consideration:

- I. Draft policy: Promotion of dissemination of information from NIH funded research
 - a. From an academic perspective, disclosure of clinical trial results is currently done in a number of ways including registration and results data reporting of an "applicable" clinical trial in the Clinicaltrials.gov database; presentation at scientific meetings and publication in scientific journals. Currently, under the federal law, i.e., Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA), results data reporting for e.g. NIH-funded trials that are "applicable" clinical trials under FDAAA are required to be publically available within one year after the primary completion date. Completing results reporting is a great undertaking for the responsible party and/or ancillary staff assisting in the review and analysis of data. Available resources and time available to analyze clinical trial data greatly differs for academic

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medical centers compared to industry. We strongly encourage modifying the reporting requirements and consider extending the reporting requirement to be completed within e.g. 24 months after the primary completion date or provide other options or mechanisms for reporting clinical trial results.

II. Other considerations

- a. Consider providing additional clarification, guidance and/or other provisions for when a grantee is awarded funds for multiple studies and how best to manage results reporting and potential impact on funding if some studies are complete and others are ongoing.

We appreciate the opportunity to provide information regarding this matter. If we can provide additional insight in your efforts to increase transparency in clinical research, please do not hesitate to contact Matthew Hodgson, MA, MS, CHRC, CCRP at the Children's Hospital of Philadelphia Research Institute at HODGSONM@email.chop.edu.

Sincerely,

Matthew Hodgson, MA, MS, CHRC, CCRP
Director, Office of Research Compliance and Regulatory Affairs

From: [Wilson, Diane](#)
To: [clinicaltrials.disseminationpolicy](#)
Cc: [Ashton-Miller, James](#); [Hutchinson, Raymond \(Ray\)](#)
Subject: University of Michigan Response to NIH Draft Policy on Clinical Trials Registration and Results Reporting
Date: Monday, March 23, 2015 8:56:01 PM
Attachments: [U.Michigan NIH Policy response.pdf](#)

Dear Office of Clinical Research and Bioethics Policy:

Attached please find the University of Michigan's response to the draft policy promulgated by NOT-OD-15-019.

Thank you for this opportunity to provide our input to the policy-making process.

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dlehman@med.umich.edu

Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues

Office of Clinical Research and Bioethics Policy
Office of Science Policy, NIH,
via email at clinicaltrials.disseminationpolicy@mail.nih.gov.
March 23, 2015

NOT-OD-15-019: NIH DRAFT POLICY ON CLINICAL TRIALS REGISTRATION AND RESULTS REPORTING

Thank you for the opportunity to respond to the NIH Draft Policy on Clinical Trials Registration and Results Reporting. We write on behalf of the University of Michigan Office of Research and the Medical School Office of Regulatory Affairs.

The University of Michigan's research portfolio exceeds eight hundred million dollars per year in federally sponsored programs, of which more than two thirds comes from the National Institutes of Health. Clinical research conducted at the University of Michigan is responsible for important scientific advances in a variety of fields, and it includes a large number of clinical trials that are conducted to evaluate new drugs and agents, new devices, new treatment regimens, and new strategies for the treatment and prevention of disease. We share the National Institutes of Health's goals of improving public health by supporting research, caring for patients, training new generations of scholars, and sharing broadly the results of those endeavors. Nonetheless, we have serious reservations about implementing the draft policy at the same time that the proposed regulations become effective.

By separate transmittal to the federal website, we have submitted our comments on the NPRM, which included a restatement of our response below. Here we share a more detailed articulation of our response to the draft policy.

While we appreciate and support the policy's intent to "support[s] the NIH mission to advance the translation of research results into knowledge, products, and procedures that improve human health", we do not see strong evidence indicating that this policy would, in fact, support that mission more efficiently or effectively than (1) maintaining the set of "encouragements" to register and report that is currently in place, or (2) simply requiring that all NIH supported clinical trials register in ClinicalTrials.gov but not necessarily be required to post results.

NIH's role in training and supporting researchers around the country is well-known and greatly honored. Similarly, the academic researcher's whole *raison d'être* is to discover, develop, and share breakthroughs that can help human health. So the fundamental goal of sharing results is one we wholeheartedly endorse.

However, academic medical researchers are pulled in many directions simultaneously, and they juggle substantial tasks, often with less structural support than do industry or government in-house researchers. As individuals, they are likely to have roles within each of their institutions' multi-faceted missions of student education, clinical care, and research (as well as community service). Therefore, prioritizing "quick turnaround" deadlines for small scale pilot studies that don't test

commercially available drugs or devices could actually require work of minimal value at the expense of patient care, medical education, or the careful design of the next research project. The ripple effects may very well serve to detract from, rather than advance, human health.

No Cost Benefit Analysis Has Been Put Forth to Justify the Draft Policy

Our concerns with the NIH policy fall primarily under the concern that no true cost-benefit analysis has been advanced to justify the great expenses involved. Whereas the NPRM is required by federal law to outline the time costs to the researcher of complying with the regulation, the NIH policy is not required to meet any such obligation. Nor does it appear to have done so.

The costs are large: At least four sets of cost have not been discussed in promulgating the draft policy:

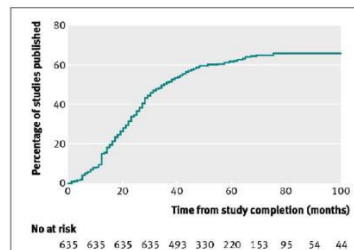
- 1) Additional NLM staff required to process 500-600 trials per year: If each trial result takes 3 hours of QA staff time, this alone is essentially another FTE – and could easily be more (500-600 trials was the range given by Valery Gordon, Acting Director, Clinical Research Policy, Office of Science Policy, NIH on January 15, 2015 in PPT entitled Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.)
- 2) 30,000 hours per year of researcher and biostatistician time nationally would be required to input those results (NPRM estimate of 50 hours for results reporting and related updates x 600 trials per year; Federal Register / Vol. 79, No. 225 / Friday, November 21, 2014 p. 69663)
- 3) Thousands of hours of additional university institutional time to design or reconfigure systems to manage, support, and monitor compliance with the new policy
- 4) Additional NLM and university time to address the special circumstances arising from including behavioral trials in ClinicalTrials.gov results – for which the system was not initially designed

Weighing these costs is not simply a matter of saying, “What is the financial cost involved to hire the labor to accomplish these tasks?” Far more importantly, the question that has not only gone unanswered but unasked is, “What is the opportunity cost – could these health and research related energies better advance human health by being employed elsewhere?” There are many reasons to believe that, if this were analyzed more carefully, the resulting decision would be to continue the current NIH practice of “encouraging” but not requiring results reporting.

To begin to try to answer this question, or at least to pose it carefully, we start with a look at the rationale for the proposed NIH policy. The preamble to the policy states, “Traditionally, scientists fulfill their obligation to the general body of knowledge through peer reviewed journal publications. However, journal publication is not always possible, and many clinical trials are not being published or published in a timely manner. A recent study found that less than half of NIH-funded clinical trials had been published in a peer-reviewed biomedical journal within 30 months of trial completion.” But that very data contains flaws that call into question the validity of the implied need. First, they are several years old. Second, the arbitrary focus on a 30 month time frame, rather than a longer window, creates the misimpression that “less than 50% publish”, when ultimately nearly two thirds do.

Publication of Clinical Trial Results

Less than 50% of NIH-funded clinical trials are published within 30 months of completion



Source: BMJ 2012;344:d7292.

2

The problem is smaller than it seems. The statement that “less than half of NIH-funded clinical trials had been published within 30 months of trial completion” is quoted in the background section of the proposed policy as justification for this policy and originates from Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in Clinicaltrials.gov: cross sectional analysis. BMJ. 2012; 344:d7292. This has been used to raise alarm bells about transparency, but the very same article, when read in full, belies the core “alarm”. It noted that “Trials completed in either 2007 or 2008 were more likely to be published within 30 months of study completion compared with trials completed before 2007.” The world of public information-sharing has expanded enormously since that time, and even the article noted the more positive trend that “54% of NIH supported trials completed in 2007 or 2008 were published in less than 30 months.” (emphasis added) It also noted that “after a median of 51 months after study completion/ a third of NIH funded trials remained unpublished”, meaning that two thirds were published with no NIH policy requirement in place! Thus, a “solution” is being proposed which will require an average of 50 additional hours of work for every NIH funded study, but which, in fact, is only “needed” for less than one third of NIH funded studies.

The solution could be worse than the problem. At the very least, before imposing such a requirement, ought there not be a follow up analysis performed to see if those publication numbers have continued to improve as the article suggested they were beginning to do? If they have, and the trend is in the right direction, why implement a policy when voluntary behavior is already improving? Indeed, such a move could actually be counterproductive by distracting researchers from issues that more directly affect human safety, data integrity, and rapid advancement of scientific discovery.

The policy may actually discourage some health research. Innovative investigators who spend hundreds of hours pursuing scientific discovery, even while they may be providing urgent clinical care, are neither inspired nor invigorated by requirements to shape all data into the same size boxes. Even if others are hired to do some of that data entry, the researchers are still held responsible. Further, only those institutions that are large enough to support a solid infrastructure will be able to continue to seek these funds. How many inventions and discoveries will be lost because scientists can no longer keep up with the demands of ever-increasing unfunded federal mandates?

Early publication of some studies’ data may be more misleading than helpful. It bears noting that many pilot studies funded by NIH are intentionally designed to be small in order to engage in discovery that will help design better subsequent studies or trials with sufficient power to be meaningful and reliable. So some portion of the one third of trials referred to in the Ross article

which were not published within 4 years, might have been the pilots or foundational trials for larger trials that are or will be published soon after their completion. Requiring the results data from such pilots to be posted in ClinicalTrials.gov might confound rather than enhance public understanding and would certainly divert energy which could otherwise go more directly toward the larger, more material studies.

Similarly, for those studies that are unable to enroll sufficient numbers to support the statistical design, reporting those (underpowered) results will not add much to scientific knowledge and could be potentially misleading. Even NIH sometimes decides that trials or studies are not able to justify further investment in them in a particular form (e.g., National Children's Study, as announced by Francis Collins Dec. 12, 2014, and reported in <http://www.nature.com/news/nih-ends-longitudinal-children-s-study-1.16556>). When trials do not come close to achieving their original goals, given that contact information is already available in the ClinicalTrials.gov database, wouldn't registration alone be sufficient to allow those who are truly interested to find out more if they need to? There is already a multiplicity of requirements for detailed data sharing from NIH and within the scientific community. Is the ClinicalTrials.gov level of "formatted high level data" really a one-size-fits-all solution that will be an efficient way to improve scientific discovery?

Draft policy potentially undermines human subject privacy. Note, although it is not mentioned in the NIH draft policy, one would hope that the NIH policy would allow for waivers of results reporting in cases where circumstances may pose a risk to human subject privacy. Even the NPRM commentary suggests that privacy concerns might be an acceptable reason for waiver of results reporting. Since, for many NIH pilot studies, sample size may be as small as 20, then the 5% threshold for adverse event reporting could result in posting individual level data, which given geographic indicators might be quite easily re-identified.

Other NIH policies already accomplish most of this goal. Other NIH policies already require more effective and complete data sharing among members of the scientific community who can most effectively leverage that data for future advances in science and medicine. The Public Access policy requires all NIH funded published literature to be freely available to the public in a reasonable time frame. A more cost effective means to achieve nearly the same goal as this draft policy would be to simply require all NIH supported human subjects research to register in ClinicalTrials.gov and link to the published articles (given that those are already required to be freely available via Pub Med Central). By so doing, NIH would acknowledge the value of peer-reviewed publications, and not ask researchers nationwide to engage in the re-work necessary to wedge their data into ClinicalTrials.gov formats. When we asked an NIH staff person about this duplication of effort, s/he responded that not all articles are written for the lay public. This argument is somewhat ironic given that a 16 year old's access to articles is used as a primary justification for the Public Access requirement. S/he also suggested that articles "tell a story", and ClinicalTrials.gov just shares the results "neutrally". But, if the point is that article publication is secondary to the importance of posting "neutral" results in ClinicalTrials.gov, then the purported low publication rates which were touted as a reason to require ClinicalTrials.gov sharing would be irrelevant. The two arguments are inconsistent.

ClinicalTrials.gov data is not necessarily reliable. Unfortunately, "neutral results" in clinicaltrials.gov can easily mislead the public.

A particularly egregious case comes to light from the work of Professor Charles Seife of New York University in his recent article in JAMA "Research Misconduct Identified by the US Food and Drug

Administration Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature” *JAMA Intern Med.* doi:10.1001/jamainternmed.2014.7774 published online February 9, 2015. In this piece, the author notes that

Eight of 16 FDA inspections of sites involved in a clinical trial of rivaroxaban, a novel anticoagulant, had been rated OAI [Official Action Indicated]. These inspections had uncovered evidence of various transgressions, such as “systemic discarding of medical records,” unauthorized unblinding, falsification, and “concerns regarding improprieties in randomization.” Consequently, the entire study, RECORD 4 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep-Venous Thrombosis and Pulmonary Embolism 4), was deemed unreliable by the FDA. (p. E4)

Professor Seife noted that publications about this trial did not mention the FDA findings. In fact, RECORD 4 is NCT00362232 on ClinicalTrials.gov, and, in the Limitations and Caveats section where the public would hope to find “Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data”, no information is provided at all, let alone information relating to the FDA finding that the study results were unreliable. Thus, it is far from clear that ClinicalTrials.gov presents a cleaner or more complete story that will help the public discern which data is reliable and which is not.

The hidden costs of the policy may hurt public health more than help it. The “stewardship of government resources” argument, is often used to bolster the “transparency” argument (i.e., public funds were used, so the public has a right to know). However, it does not seem fiscally responsible to create a new policy that will require hundreds of grant recipient institutions to each spend hundreds of hours on infrastructure to facilitate compliance, plus thousands of government staff hours to be spent designing and maintaining systems to monitor compliance – especially when most study results will be available in a number of other formats. With each additional policy add-on, costs of doing research climb (whether paid for by NIH or by the institution), ultimately increasing taxes or health care costs (as research gets subsidized by clinical care) or both, or diverting funds from other more meaningful forms of health care enhancement. With each elected administration claiming it will reduce regulatory burden, these increases in policy requirements arguably decrease rather than increase public confidence in the entire system.

Recommendation: Either wait until the NPRM has been implemented and perform a thorough cost-benefit analysis, or adopt a more finely tuned policy. If the NIH proposed policy simply required that all NIH funded trials register in ClinicalTrials.gov, we would endorse it wholeheartedly. There would be minimal additional cost because the registration and its concomitant ClinicalTrials.gov Quality Assessment takes a small fraction of the time that results reporting takes, and the vast majority of researchers already register any such studies because of their desire to publish in journals which follow International Committee of Medical Journal Editors policy. We believe that the NIH and the nation’s public health would be better served by allowing the ClinicalTrials.gov regulations to be finalized; continuing the current NIH policy of “encouraging” registration and results reporting; and allowing the more critical drug and device trial reporting changes of the NPRM to become fully implemented before imposing a policy of results reporting on other NIH funded trials. An alternative targeted and efficient approach would be to require that all NIH funded research must, within three years of study completion, either (1) have a larger, follow up study underway, (2) have published results, or (3) post results in ClinicalTrials.gov.

The Draft Policy does not recognize the time and effort required to register and report results for clinical trials in ClinicalTrials.gov. Furthermore, there is a lack of recognition of the ongoing time commitments involved in maintaining compliance with FDAAA Section 801 and the NPRM as currently written. The proposed policy for requiring registration and results information for all NIH-funded clinical trials and the additional delineation that all clinical trials would be subject to the forthcoming proposed rule-making under FDAAA, do not account for the significant impact of financial and time obligations required by investigators and institutions to comply with this unfunded mandate.

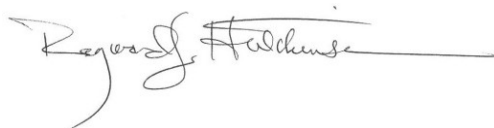
Recommendation: We request that both the NIH and the FDA further recognize the time and effort required for both updating current study records and the ongoing updates that will be required under the proposed policy changes. We suggest that additional consideration be made regarding the financial obligations that will be incurred by academic medical centers to ensure compliance of investigator-initiated research as necessitated by these proposals. We request that the NIH allow the time and effort required for ClinicalTrials.gov compliance to be included as a direct-cost on NIH grants.

Again, we thank you for the opportunity to respond to the proposed policy. We look forward to continuing to work with NIH in continued service of expanding knowledge and discovery to serve our nation's health.

Sincerely,



James Ashton-Miller, Ph.D.
Associate Vice-President for Research
University of Michigan Office of Research



Ray Hutchinson, M.D., M.S.
Associate Dean for Regulatory Affairs
University of Michigan Medical School

March 23, 2015

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. NIH-2011-0003 and RIN 0925-AA52; Clinical Trials Registration and Results Submission; Proposed Rule; Request for Comments

AND

Notice Number NOT-OD-15-019: NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

Dear Sir or Madam:

The Medical Device Manufacturers Association (“MDMA”) appreciates the opportunity to comment on the National Institutes of Health (NIH) Proposed Rule and Request for Comments on Clinical Trials Registration and Results Submission and the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

MDMA is a national organization representing the innovative, entrepreneurial sector of the medical technology industry. MDMA’s mission is to ensure that patients have access to the latest advancements in medical technology, most of which are developed by small, research-driven medical device companies. As such, MDMA is particularly sensitive to ensuring that the appropriate incentives are in place to promote innovation and attract investment. According to the Department of Commerce, 80 percent of medical device companies have fewer than 50 employees and 98 percent have fewer than 500. The unintended consequences of NIH’s proposed rule and draft policy would significantly harm smaller companies by forcing public release of proprietary and confidential commercial information.

A number of the issues included in the proposed rule and draft policy were discussed and debated by Congress during the passage of the Food and Drug Administration Amendments of 2007 (“FDAAA”). At the time a robust discussion occurred which included drawing a significant distinction between the manner in which drugs and medical devices are developed. The rationale for the delayed disclosure provision as passed was a recognition of the importance of protecting proprietary clinical trial information in the competitive device environment because patents provide little protection for devices. In contrast to drugs where entire molecules are frequently patented, engineering or design changes can readily negate device patents. As a result, the effect of early disclosure of proprietary clinical trial designs can be significant – allowing better capitalized companies to “leapfrog” over their smaller competitors. Small companies account for the vast majority of device innovation and contribute

greatly to maintaining competitiveness across the industry. In short, better capitalized competitors could potentially speed a competing device into clinical trials and obtain final FDA clearance or approval in order to take advantage of the benefits associated with being first to market. The proposed revisions would have the unintended consequence of reducing patient access to new device innovations and eliminating many small device companies from the marketplace.

The medical device industry is aligned on the key issues and MDMA strongly supports the more detailed comments filed by the Advanced Medical Technology Association (“Advamed”) on March 20, 2015.

In closing, MDMA appreciates this opportunity to comment on this important issue and looks forward to working with interested parties to ensure that any potential modifications to the clinical trial registry system do not adversely impact small innovators, patient care and the delicate medical technology innovation ecosystem.

Respectfully Submitted,

A handwritten signature in dark ink, reading "Mark B. Leahey", with a long horizontal flourish extending to the right.

Mark B. Leahey
President & CEO
Medical Device Manufacturers Association

March 23, 2015

Docket No. NIH-2011-0003

RIN 0925-AA52

Office of Clinical Research and Bioethics Policy,
Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Comment on the NPRM and the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

I write to comment on the National Institute of Health's Notice of Proposed Rulemaking as published at 79 Federal Register 225 (November 21, 2014) as well as the proposed policy changes promulgated the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. I have worked with clinical trials for four years in my capacity as a Regulatory Specialist. I commend the ClinicalTrials.gov staff for their dedication and helpfulness. They have provided very useful Train the Trainer workshops, and they have worked very collaboratively with those of us in academic medical centers who are close to the front lines of compliance.

I write both as a worker in the field, but also as a citizen and a taxpayer, with elderly relatives and familiarity with friends and former students who have less access to health care than I do. While I feel deeply sympathetic to the many families of cancer victims who commented on the NPRM about the importance of posting clinical trials materials as soon as possible. I, too, have lost relatives to cancer, but I may be less confident that more data on public websites will make more and better health care available to more people. Indeed, seeing the vast and ever-growing sums that are spent on IT infrastructure in business and government, as well as health care, I am personally quite skeptical that the rapid expansion of systems like Clinicaltrials.gov is a wise use of government time and resources.

Part I. Notice of Proposed Rule Making Document

1. I do not think that the expansion of ClinicalTrials.gov results reporting to all Applicable Clinical Trials is an advisable or necessary step. I think that it will be expensive to manage and adjudicate all of the various extensions that industry will request for future FDA applications. Thus, I think maintaining the present system of only requiring results reporting for Applicable Clinical Trials of drugs and devices when they are FDA approved and therefore accessible to the public is a more prudent use of government resources.
2. The concept of lay summaries is very appealing, but it is hard to imagine how pharmaceutical industries will avoid the temptation to use them promotionally, and it would require serious diligence on the part of government staff to watch out for these concerns. I support the continued deferral of any **requirement** for technical or non-technical summaries. Creating

fields for voluntary technical or non-technical summaries as a small pilot would be a reasonable option.

3. **Submission of full protocols.** I think that full protocol submission would vastly complicate public access to data rather than improve it. The current information detailed by registration and results summary submission of data elements for clinical trials is sufficient to meet the goals of the statute. Version control with protocols can be extremely difficult to manage even for IRBs. The costs in labor and money of managing a system with a million protocols, a number which is not inconceivable in another decade, (given the size of ClinicalTrials.gov and the fact that many protocols go through many versions over the course of a trial) seems hard to reconcile with fiscally responsible government. The necessity for careful, appropriate redactions complicates this possibility still further.

4. **Increasing the Time Period for Submitting Results Information to 18 months**

The proposed rule should be modified in section 11.44 (a) to allow 18 months (rather than 1 year) after the primary completion date to report results, and NIH, if it moves forward with its policy, should consider creating other standardized exceptions or delays for those non applicable clinical trials for which a plan of publication is in process. Researcher physicians have so many obligations. They work incredibly hard. In the six years since the results modules have been up and running, the estimates of how long it takes to post results in clinicaltrials.gov has doubled from 25 to 50 hours of work. We should allow professors who also teach, care for patients themselves, and serve on many local and national committees and boards, to have a little more flexibility to accommodate this substantial increase in their workload. The more reasonable the government is in its expectations, the more likely compliance will rise. As was illustrated in the classic *The Little Prince* by Antoine de St. Exupery, even a monarch must keep his commands within the bounds of reason.

5. **The proposed regulations promote a mixture of 30-day and 15-day windows for various sorts of updates and corrections. This is confusing; it makes it harder for well-meaning scientists who are not themselves regulatory geeks to comply. Recommendation:** A uniform 30-day standard window for all short-term deadlines should be adopted. Shorter windows do not seem likely to provide increased benefit to information seekers. With the contact information available in Clinicaltrials.gov, persons who urgently seek the latest information about a particular trial can write to the source directly.

6. **Results information.** Please don't make Responsible Parties who have successfully completed modules of results information for some or all primary outcomes, go back and add new data field information to those trials, just because they may have some secondary outcome data left to add. If you impose continued system improvement incrementally on newly submitted trials only, researchers will be less frustrated and give better effort toward compliance than if they feel that compliance with ClinicalTrials.gov is a Sisyphean task, where every time they get the ball almost up the hill, new rules roll it back down. .

Responses to a few specific provisions of the proposed rule

1. § 11.10 *Completion date* –

Recommendation 1: Please keep using the term “Primary Completion Date” A PRS-specific definition of simply “Completion Date” may cause confusion. “Primary Completion Date” is recognizable to current users of the system and is a term whose definition is less likely to be “assumed” and misinterpreted by experienced and inexperienced PRS users.

Recommendation 2: Thank you for clarifying that for clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes.

2. § 11.10 *Study Start Date* – Please switch to calling this field “Date of First Enrolled Participant”, instead of “Study Start (anticipated and actual)”. Because for other purposes, such as human subjects protection, IRBs consider studies to have “started” when they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled, the inconsistency among definitions of the proposed term will confuse many parties more than it will help researchers comply.

3. §11.28(c) *Expanded Access Records* – Please make these the responsibility of the manufacturers of the expanded access product or the Expanded Access IND holder. If additional links to clinical trials are needed, it seems like Clinicaltrials.gov could do this for the public.

4. §11.35 and 11.52 When will NIH post submitted information (for registration and results)?

Please do not post information of any sort that the government believes to be inaccurate or misleading, or simply inadequately clear. If information has not at least passed the Clinicaltrials.gov QA, it should not be published on ClinicalTrials.gov. Doing so would be highly irresponsible. There are plenty of other ways to push Responsible Parties to be timely in responding to QA comments. (And sometimes the delays are government-caused, as after the shut down 18 months ago. But still, it’s better for the data to go public late than for it to go public wrong. Imagine if someone posted in the newspaper that you done something embarrassing because they hadn’t been able to reach you to get your “correction” as quickly as they wanted to. The damage caused would far outweigh the benefit of speedy news in general.)

5. §11.64 Updates to Clinical Trial Information Submitted to ClinicalTrials.gov

Recommendation: Please streamline all requirements to two sets of timeframes: 30 days for urgent matters and annual updates for everything else. These are permitted in the law and are much more efficient for researchers to follow.

II. NIH Draft Policy on Clinical Trials Registration and Results Reporting.

Investigators conducting independent research at academic medical centers will be severely impacted by the policy as currently proposed, requiring all clinical trials under the new NIH definition to register and report results in Clinicaltrials.gov within 12 months of completion. More than half of the NIH funded trials will be required to register and report results under the NPRM anyway, and others will at least register based on their authors' desire to publish. This should be adequate. There should be an exception granted to small pilot trials that serve as the basis for larger, statistically reliable trials. With "full size trials", NIH should allow publication as an alternative to results reporting for trials that don't fall under the NPRM. That option, along with a 30 – 36 month window, rather than a 12 month window would be a reasonable compromise to see that all NIH funded work gets out to the public, without placing an unfunded, unreasonable 50 hour tax on all studies, large or small. IF the NIH policy is adopted as planned, rules should be clarified to allow for direct costs to be assessed to the grant for those hours of data entry.

III. Additional Comments and Limitations of ClinicalTrials.gov Website and Protocol Registration System Communication.

Data Quality, Integrity and the Caveats and Limitations Data Field:

This field **currently has a 250 character limit**. This is not nearly enough to describe any serious concerns or nuances about the data. We should be encouraging the use of this field as one of the most important in the whole ClinicalTrials.gov and possible even asking, when it is blank, why is it blank? Are there no imperfections or questions that arose during the course of the trial that give the researcher reason to caution the public about the conclusions to be drawn?

Recommendation: Please expand the caveats and limitations field to at least a 200-word field to allow for careful and nuanced explanation of these concerns.

Sincerely,

Diane Lehman Wilson



Comment from Jeffrey Drazen, New England Journal of Medicine

This is a Comment on the **National Institutes of Health (NIH) Proposed Rule: [Clinical Trials Registration and Results Submission](#)**

For related information, [Open Docket Folder](#)

Comment Period Closed

Mar 23 2015, at 11:59 PM ET

Comment

The Editors of the New England Journal of Medicine submit comments on the following topics regarding the NPRM for review:

1. Topic: Feasibility Studies [11.22(b)]. Feasibility studies are not well defined and yet unspecified small feasibility studies may be exempt from the device applicable clinical trial algorithm. We think that any study in which a persons medical care results from assignment within the context of a clinical trial, in which there are 10 or more participants, should be registered and subject to the same regulations as any other interventional study.
2. Topic: Definition of Controlled [11.10]. We agree that any interventional trial in human subjects should be considered a controlled trial. Clearly any trial with two or more arms is a controlled trial (regardless of whether the chosen comparator arms are the most scientifically appropriate). A one-arm study is presumably using some historical control or baseline measure, and therefore should still be considered a controlled study. There are important examples of first in man exposures that yielded important scientific knowledge even without classic parallel controls. If for some reason, a change in the definition of controlled is not adopted, at a minimum, an explanation for why an interventional trial is not being considered controlled should be provided.
3. Topic: Unapproved Devices [p69576]. To avoid the burdensome requirement that investigators register trials of unapproved devices in [clinicaltrials.gov](#) and a separate registry to meet ICMJE requirements, investigators should be allowed to voluntarily agree to the release of relevant data by [clinicaltrials.gov](#) in order to avoid duplicate posting.
4. Topic: Timing of Submission of Trial Results [11.44]. Currently, submission of trial results can be delayed for several years after completion of the trial. Consider shortening this time period to no more than one year. In cases where parties choose to make information public in the form of an abstract, advertising, or other public communication, full results should be submitted to [clinicaltrials.gov](#) within 30 days of that release to avoid dissemination of incomplete and potentially misleading information.
5. Topic: Narrative Summaries [p69581]. Recognizing the immense challenge of establishing a review mechanism to evaluate every proposed narrative summary, we think that narrative summaries should NOT be included in [clinicaltrials.gov](#).
6. Topic: Protocol Submission [p69582]. We agree that the collection of full protocols by [clinicaltrials.gov](#) could be of important benefit. Protocols should be submitted by the time of results reporting, if not sooner. Collection of protocols at the time of trial registration could be considered, assuming that any proprietary information may be redacted and that the NLM can develop appropriate mechanisms to keep protocols secure until their public release.
7. Topic: Quality Review Process [p69586]. Completion of the quality review process should be required prior to public posting of information. The public does not benefit, and may be harmed, by the dissemination of misinformation.
8. Topic: Adverse Events [p69590]. It is impossible to assign causality to adverse events; therefore, all adverse events should be reported without attribution to the intervention. Because accurate information regarding the number of deaths that occurred in each arm of a trial is critical to understanding and interpreting the trials results, we agree that all-cause mortality must be included as part of the results of every trial.
9. Topic: NIH definition of Clinical Trial. NIH policy should be applied to all interventional studies with human participants regardless of outcome type (including PK, phase-0, and phase-1 studies).

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New England Journal of Medicine

From: [Josh Leslie](#)
To: [clinicaltrials.disseminationpolicy](#)
Subject: Stewardly's Comments on NOT-OD-15-019
Date: Tuesday, March 24, 2015 2:39:08 AM
Attachments: [StewardlyResponseToDraftNIHPolicy-NOT-OD-15-019.pdf](#)

Dear Office of Clinical Research and Bioethics Policy, Office of Science Policy, NIH:

Thank you for the opportunity to review and comment on the Draft NIH Policy for Registration and Reporting of Results for NIH-funded Clinical Trials. Enclosed you will find comments and recommended revisions on behalf of Stewardly, submitted by 11:59 PST on March 23rd, 2015.

We are not clear on whether all comments will be posted publicly. If this is the case, we are comfortable with, and consent to our comments being posted publicly, including identifiable information, with the exception of my e-mail address (unless encrypted or otherwise obfuscated). If e-mail addresses will not be encrypted for publicly posted comments, via the use of Javascript or other obfuscating technological measures, we do not consent to the publication of my e-mail address, as it will be harvested by web spiders and used by spammers to send unsolicited e-mail.

Should you require any further information or clarifications with respect to our comments and proposed revisions, I would be happy to speak with you, or offer further information in writing.

Best Regards,

Josh Leslie
Founder, Stewardly
Tel: 647-606-9604
www.stewardly.ca



Stewardly's Response to NIH Request for Public Comments

NOT-OD-15-019

Stewardly lauds the efforts of the NIH to introduce a policy to promote greater transparency of clinical trial results, and expand the number of trials for which information is posted and maintained in publicly-accessible clinical trial registries. With that said, while we agree with much of this draft policy as-is, there are several issues with the current draft that we would like to raise for NIH's due and thoughtful consideration. For clarity, we have stratified our comments below as "substantive" or "administrative".

Substantive Comments

Issue #1 —The requirement to report adverse event information to a clinical trial registry

If implemented, the requirement to report adverse event information to ClinicalTrials.gov (or any other publicly-accessible clinical trials registry), has broad-reaching implications, including but not limited to, a greatly increased administrative burden on sponsors and researchers, with no evident benefit or justification.

The FDA has the requisite expertise and access to unblinded data (as needed) to meaningfully interpret adverse event information from clinical trials of regulated health products, as well as the regulatory mandate to do so. For clinical trials not within FDA's (or a comparable regulator's) purview, unless an equivalent body has been identified, and will be mandated and supplied with sufficient resources and access to unblinded data (as needed) by NIH to undertake a meaningful analysis of reported adverse events, we expect that a requirement to report adverse events to a clinical trial registry may do more harm than good. We assert that there is a high likelihood of reported adverse events being misconstrued or misinterpreted by the general public, if this requirement remains as-is in the final policy, with no effective mechanism established to meaningfully analyze reported adverse events.

See section IV. B., from OHRP's [guidance on unanticipated problem reporting](#) for a brief exposition of the problems that can arise from adverse event reporting. These issues are explored in greater detail in sections "I. INTRODUCTION" and "II. BACKGROUND" of the FDA's [guidance](#) on the subject.

If this requirement is to be included in the final policy, we would recommend that at a minimum, the wording be changed to "unanticipated problem" and that the established OHRP definition of "unanticipated problem" be used/referenced.

NOT-OD-15-019**Issue #2 — The definition of “clinical trial” used in the policy**

We would question why the draft NIH policy introduces a different definition of “clinical trial” than is already found in the [WHO International Clinical Trials Registry Platform \(ICTRP\)](#), which follows below:

"For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials."

To increase the consistency with which clinical trials are registered worldwide, and to simplify the process for sponsors, researchers and research organizations in determining which trials require registration and which trials do not, we would propose that the WHO ICTRP definition of “clinical trial” be used in this NIH policy, or that the use of a different definition be explicitly justified and explained.

Issue #3 —The requirement to use ClinicalTrials.gov exclusively for trial registration

Federal granting agencies in other countries can, and do, mandate the public registration of clinical trials, and maintenance of data regarding same, in clinical trial registries other than ClinicalTrials.gov. Accordingly, it is common in such countries for research organizations to have established processes and procedures for completing reporting to specific clinical trial registries (e.g. - [ISRCTN](#) as one example, acceptable to Canadian granting agencies).

Given that the intent of this policy is to ensure public registration of, and availability of key information regarding, clinical trials, it would seem that registration in publicly-accessible clinical trial registries other than ClinicalTrials.gov also could be seen as satisfying this requirement. As such, rather than requiring significant duplication of effort in registering trials in multiple registries, for NIH-funded trials in countries outside of the United States, we would ask that the NIH give due and equitable consideration to accepting the registration of trials in other publicly-accessible clinical trial registries as satisfying the requirements of this policy.

In considering this, it is important to note that other clinical trial registries may not have fields over and above the current 20 items mandated in the WHO Trial Registration Data Set (TRDS) — Version 1.2.1 as of the date of these comments. In light of this fact, if other

Stewardly's Response to NIH Request for Public Comments

NOT-OD-15-019

publicly-accessible clinical trial registrations are acceptable to NIH, we would propose that the minimum standard for such registrations be [the current WHO TRDS](#) at the time of trial initiation (≤ 21 days after enrollment of the first participant).

As an example of granting agency requirements in other countries on this subject, please see the relevant excerpt below from [the current Tri-Council Policy Statement 2 \(TCPS2\)](#), the Canadian requirements for organizations receiving federal Canadian research funding:

“Article 11.3

All clinical trials shall be registered before recruitment of the first trial participant in a publicly accessible registry that is acceptable to the World Health Organization (WHO) or the International Committee of Medical Journal Editors (ICMJE).

Application

Clinical trial registries are intended to increase transparency and accountability by providing a record of clinical trials at the recruitment stage that can be used to locate publications of trial results (see Article 11.12). This helps prevent publication bias, that is, the selective publication of only those trials that yield results in support of an intervention. These registries, in addition to agency policies, editorial policies, ethical policy reforms, and revised national and institutional ethics policies and results disclosure requirements, contribute to a multi-faceted approach to eliminate non-disclosure. The collective goal is to reduce publication bias, and prevent the suppression of data in clinical research.

Clinical trials shall be registered in a publicly accessible registry that is acceptable to the World Health Organization (WHO) or the International Committee of Medical Journal Editors (ICMJE). All fields outlined in the WHO Trial Registration Data Set (TRDS) must be completed in order for a trial to be considered fully registered. A registration with missing information or uninformative fields in the TRDS is unacceptable. Researchers shall provide the REB with the number assigned to the trial upon registration.”

Issue #4 — Additional administrative burden and trial costs introduced by this policy

This draft policy introduces responsibilities for sponsors, researchers and research organizations that will require substantial time and resource commitments to adhere to. Will NIH grants post-introduction of a final policy, include allowable costs related to clinical trial registration?

Stewardly's Response to NIH Request for Public Comments
NOT-OD-15-019

Administrative Comments

“Responsibilities”, 1st sentence — We believe that the word “accord” in this sentence should be replaced with “accordance”.

“References”, #7, 1st sentence — As currently drafted, this sentence appears to have superfluous words included. Proposed redraft:

“The meaning of several terms within the NIH definition of clinical trial, are further defined as follows.” *(Note: this suggestion may no longer be relevant if our substantive comments with respect to the definition of “clinical trial” are accepted and incorporated by NIH)*



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1111 Franklin Street, 11th Floor
Oakland, California 94607-5200

March 20, 2015

[Submitted electronically via www.regulations.gov]

Re: Notice of Proposed Rulemaking (NPRM) for Clinical Trials Registration and Results

Submission (RIN 0925-AA52, Docket Number NIH-2011-0003)

Jerry Moore, NIH Regulations Officer, Office of Management Assessment

[www.regulations.gov]

Re: Proposed NIH policy on Dissemination of NIH-Funded Clinical Trial Information

(NOT-OD-15-019)
Office of Clinical Research and Bioethics Policy, Office of Science Policy, National Institutes of Health [clinicaltrials.disseminationpolicy@mail.nih.gov]

I am writing on behalf of the University of California system (that comprises schools of medicine at Davis, Irvine, Los Angeles, Riverside, San Diego and San Francisco) to offer comments on the National Institutes of Health (NIH) Notice of Proposed Rulemaking regarding requirements for submitting registration and results information to clinicaltrials.gov (Proposed Rule).

The University of California (UC) is grateful for the opportunity to offer comments and recommendations to NIH on the Proposed Rule to promote transparency in clinical trials, enhancing patient access to trials, as well as enhancing understanding of the results of clinical trials. We support the proposed requirements for clinicaltrials.gov registration and results



reporting, but share all of the concerns expressed by our sister campus, UCSF, regarding the administrative burdens the proposed rule represents and fully support the recommendations and comments in their letter regarding this proposed rule. Therefore, the UC systemwide comments in this letter mirror those conveyed by UCSF in its February 17, 2015 comment letter on the above-referenced NPRM and proposed policy.

UC supports many of the proposed requirements for ClinicalTrials.gov registration and results reporting, however we identified a number of proposed rules that would benefit from additional clarification, and a few issues that merit further consideration.). Three of UC's 5 medical center campuses have moved to a centralized Protocol Registration System (PRS) whereby a central office administers an institutional account and allocates access to individual Principal Investigators (PIs). The PRS administrators at our UCSF medical center campus currently oversee approximately 1,000 records, and their experience implementing the existing regulations informed our systemwide comments on the proposed rules.

I. Comments on specific provisions of the NIH NPRM document.

Due to the breadth of the NPRM, we limited the scope of our comments to the proposed rules



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that represent our greatest areas of concern. Excerpts of the relevant NPRM text are provided below for context, followed by our comments in *italics*.

Overview of Proposed Rule III- C. Key issues considered in this proposed rule

7. Submission of the full protocol (FR 69582)

The proposal to require full protocols is unnecessary because the registration and results elements required under current rules provide sufficient information for both compliance and public information. Given that protocol documents contain proprietary information, redaction standards should be established before the rule is implemented.

Overview of Proposed Rule III - C. Key issues considered in this proposed rule

9. Retroactive submission of additional results information (FR 69583)

As described in section III.D of this preamble on Effective Date, we do, however, propose to require the responsible party for an applicable clinical trial that reaches its completion date prior to the effective date of the final rule to submit all of the results information specified in proposed § 11.48 if the responsible party has not submitted results information prior to the effective date of the rule.

This proposed rule would create a significant burden for Academic Health Centers (AHCs) and investigators. UC's 5 AHC's are already expending considerable resources to support investigators' compliance with FDAAA results reporting requirements. UC's AHCs are also working through a substantial backlog of results submissions, including for studies originally registered and owned by NIH, where investigators have left the institution, retired or are deceased. The backlog includes older studies that were not designed or budgeted with awareness of FDAAA or the conservative OMB estimated 41 work hours to comply with results reporting. It is already difficult and time-consuming to retrospectively locate and summarize results data in the required format, and requiring additional information will only increase noncompliance and divert resources from other areas of research compliance.

One way to alleviate the financial burden would be to allow registration and results reporting to be addressed in federal grants budgets as direct costs to the grant, whether incurred directly by the investigator or shared with a central administration unit. Federal funding agencies should also study actual burden (as opposed to projected estimate) for assuring compliance with all registration and reporting requirements.

Overview of Proposed Rule III - C. Key issues considered in this proposed rule

12. Quality control procedures (FR 96584)

Consistent with the proposal in § 11.66 regarding correction of clinical trial information, responsible parties would be required to correct the errors, deficiencies and/or inconsistencies



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not later than 15 calendar days after being informed of them by the Agency or otherwise becoming aware of them (e.g., if they discover the errors, inconsistencies, and/or deficiencies themselves), whichever is later.

A mixture of 30-day and 15-day windows increases the complexity of understanding and complying with reporting and updating requirements. We suggest that a 30-day standard window for all deadlines is more understandable and practicable; shorter windows do not seem to provide increased benefit to information seekers relative to the costs of enforcement and compliance.

In addition to complexity posed by having windows of various duration, a 15-day window to correct errors may create a burden for investigators, and a 30-day window would be more appropriate; in many cases 15 days would be sufficient, but in cases where the changes are complex this would not allow for sufficient time to produce additional statistical output if required plus proper internal review and approval processes.

Overview of Proposed Rule III - C. Key issues considered in this proposed rule

13. Updating submitted clinical trial information (FR 69587)

Proposed § 11.64(b) identifies several data elements that must be updated not later than 30 days after a change occurs (e.g., Overall Recruitment Status and Availability of Expanded Access), requires updates to U.S. FDA Approval, Licensure, or Clearance Status not later than 15 calendar days after the change occurred, and specifies that if a protocol is amended in such a manner that changes are communicated to participants in the clinical trial, updates to relevant clinical trial information must be submitted no later than 30 calendar days after the protocol amendment is approved by the human subjects protection review board.

For updating clinical trial registration information, a mixture of 30-day and 15-day windows significantly increases complexity of understanding requirements and decreases likelihood of compliance. A 30-day standard for all deadlines would be more understandable and practicable; shorter windows do not seem to provide increased benefit to information seekers relative to the costs of enforcement and compliance.

Overview of Proposed Rule III - D. Effective Date/Compliance Date

4. Results information (FR 69593)

The Agency proposes to exercise its authority under section 402(j)(3)(D)(iv)(II) of the PHS Act in situations when partial results are due on or after the effective date of the rule to require the responsible party to submit clinical trial results information under proposed § 11.48 for all outcome measures, including primary outcome measures submitted prior to the effective date of the rule.



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Updating previously approved outcome measures that have passed NIH/PRS quality review may present a significant burden for investigators. Considering that studies completed prior to the effective date were not designed or budgeted to comply with the new requirements, some investigators may be unable to comply. Attempting to comply or explaining to PRS why compliance is not possible will be very time-consuming to investigators, PRS administrators at the institution, and PRS reviewers.

Subpart a General Provisions § 11.4

(3) *Withdrawal of the designation of a principal investigator as the responsible party.* (i) In the event a principal investigator who has been designated the responsible party becomes unable to meet all the requirements for being so designated under paragraph (c)(2)(i) of this section, the principal investigator must withdraw the designation in the form and manner specified at <http://prsinfo.ClinicalTrials.gov>, at which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section. (ii) In the event a principal investigator who has been designated the responsible party is unable because of death or incapacity to withdraw his or her designation, the sponsor will be considered the responsible party unless and until the sponsor makes a new designation in accordance with paragraph (c)(2) of this section.

Under such circumstances, we suggest the sponsor could submit a waiver of results requirements. This would allow for the record to be closed from the institutional account and posted on the public site with a notice of the reason that the study was terminated and only partial results (if any) were obtained. UC's PRS administrators have had the experience of completing results for studies that were terminated due to death or relocation of investigators. Although the studies were abandoned and no analyses were performed, there was no mechanism to remove the problem records from the institutional account. These situations cause an enormous burden on institutional resources. Much time is spent attempting to locate abandoned data and composing language that satisfies PRS reviewers, but the posted information often does not provide benefit to the public or the scientific community. Considerable PRS reviewers' time is also spent advising investigators and AHC PRS administrators through the process.

Subpart a General Provisions § 11.10

Completion date means, for a clinical trial, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date upon which data collection is completed for all of the primary outcomes.

We strongly support retaining use of the term "Primary Completion Date" since the concept that



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a study is “Completed” but can still be “Active, not recruiting” seems mutually exclusive, and a clear definition of Primary Completion Date could fulfill the same purpose. A PRS-specific definition of “Completion Date” may cause confusion and lead to posting of inadvertently incorrect information. “Primary Completion Date” is recognizable to current users of the system and is a term whose definition is less likely to be “assumed” and misinterpreted by both experienced and inexperienced PRS users.

Subpart a General Provisions § 11.10

Outcome measure means a pre-specified measurement that will be used to determine the effect of experimental variables on the human subjects in a clinical trial. See also primary outcome measure and secondary outcome measure.

We strongly suggest that the NIH provide additional resources and training to help investigators understand the particular structure and specificity required for the statement of Outcome Measures. This section triggers the most QA Comments and presents a significant burden to PRS Administrators attempting to assist investigators with registration, responding to QA comments, and results reporting.

Subpart a General Provisions § 11.10

(14) *U.S. FDA Approval, Licensure, or Clearance Status* means, for each drug or device studied in the clinical trial, whether that drug or device is approved, licensed, or cleared by the U.S. Food and Drug Administration for any use.

Approval status for the indication may be an informative option, e.g., “Approved but not for use being studied.”

Subpart a General Provisions § 11.10

(16) *Study Start Date* means the estimated date on which the clinical trial will be open to enrollment of human subjects. If the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled.

We consider studies to have “started” when they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled. ClinicalTrials.gov could call this field “Date of First Enrolled Participant,” instead of Study Start (anticipated and actual).

Subpart a General Provisions § 11.10

(20) *Secondary Outcome Measure Information* means a description of each secondary outcome measure, to include the following information: (i) Name of the specific secondary outcome measure; (ii) Description of the metric used to characterize the specific secondary outcome



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measure; and (iii) Time point(s) at which the measurement is assessed for the specific metric used.

Please clarify whether outcome measures that are not part of the analysis plan, OR indicated to be exploratory or tertiary, are not required; Zarin et al. (NEJM 2015) does not contain the “or” statement.

Our understanding is that the presence of an analysis plan does not change the nature of an exploratory outcome measure to any other outcome measure type.

Subpart a General Provisions § 11.10

(29) *Availability of Expanded Access* means, for an applicable drug clinical trial of a drug that is not an approved drug: (i) An indication of whether there is expanded access to the drug under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) for those who do not qualify for enrollment in the applicable clinical

Please clarify: Does this apply only to Expanded Access (EA) clinical trials under the same sponsor-investigator as non-EA trials using the same drug? If not, we would suggest that FDA require manufacturers to notify all investigators who are studying a drug when any EA becomes available. Would NIH recommend that Investigators seek agreement from manufacturers to provide notification of any EA records throughout the duration of the investigator-initiated trial of the same drug? Could PRS notify investigators when expanded access record is created for the same drug that they’re studying?

Subpart C Results Submission § 11.48

(v) *Statistical Analyses*. Result(s) of scientifically appropriate statistical analyses, if any, including any statistical analysis that is: (A) Pre-specified in the protocol and/ or statistical analysis plan that was performed on the outcome measure data, (B) Made public by the sponsor or responsible party prior to the date on which results information is submitted for all primary and secondary outcome measures studied in the clinical trial, or (C) Conducted in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial. Submitted Statistical Analysis information must include:

Please clarify: Will all statistical analyses – not just primary analysis – published in a manuscript be reported under criterion B, even if exploratory, post-hoc, and/or sub-group analyses? There might be hundreds of additional analyses in some cases, which could represent a very significant burden to the responsible party, particularly where reporting in PRS was not previously planned or budgeted. Furthermore, without explanatory context (which is not



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permitted) posting of exploratory or post-hoc analyses could be misleading or confusing to readers. Moreover, PRS would need major expansion to include all the possible statistical analyses this could encompass that are not current options to select in the system. Please Note Results submitted to NIH or other Federal Funders should contain sufficient information and be in a format with xml upload, or link acceptable to ClinicalTrials.gov. We suggest that ClinicalTrials.gov results reporting requirements be accepted in similar formats to reduce duplicative efforts when results are required to be reported to NIH or other Federal funders (e.g., CTRP for NCI).*

Subpart C Results Submission § 11.48

(1) *Statistical Analysis Overview*: Identification of the arms or comparison groups compared in the statistical analysis, the type of statistical test conducted; and, for a non-inferiority test, a description of the analysis that includes, at minimum, the power calculation and non-inferiority margin;

NPRM: We invite comment on whether the list of proposed options is sufficient for all applicable clinical trials or voluntarily submitted clinical trials for which statistical analysis information might be submitted to ClinicalTrials.gov under this proposed rule.

Thank you for the opportunity to comment. The structure and drop-down choices throughout the statistical analysis section appear to be too rigid and limiting to accommodate non-drug/device studies and smaller (investigator-initiated) studies. Exempting non-industry or non-drug/device studies from this requirement may be an appropriate alternative to the myriad of choices and free-text descriptions needed accommodate all types of analyses in all types of trials. In the absence of such an exemption, at minimum, a much more robust backdrop of explanations/definitions/guidance in PRS will be needed to enable individual investigators to report statistical analyses correctly, including categorizing the “Type of analysis,” without undue burden.

*The limited selections for “type of analysis” may be difficult and burdensome for behavioral trials and Phase I-II trials. Individual investigators, particularly those in social or behavioral sciences and new to ClinicalTrials.gov, may not understand how to categorize various types of analyses. Unless only superiority, non-inferiority, or equivalence analyses will be required to report results, an option is needed for “Other” type of analysis. “Not applicable” is a term commonly understood to mean that a question is not relevant to the situation. However, **any** analysis is a “type of analysis”; therefore, “Other” is more appropriate than “Not applicable” for analyses other than efficacy comparisons. Examples: variability estimate for sample size calculation of a larger RCT; trials with qualitative outcomes for feasibility and/or acceptability; trials including analyses for specificity, sensitivity, correlation, validity, reliability,*



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interexaminer reliability, etc. Please explain whether only those analyses comparing intervention to control will be required in results reporting; if not, please provide a less structured format and much more detailed guidance in consideration of non-industry, non-drug/device studies with outcomes that may not be efficacy comparisons.

Subpart C Results Submission § 11.48

(ii) Information for each table specified in paragraph (a)(4)(i) of this section must include the following elements:

(D) Total Number Affected, by Organ System

The requirement to summarize adverse events by organ-system presents a significant burden for investigator-initiated studies at AHCs:

- Investigator-sponsors usually do not have access to or use MedDRA (Organ system) to record AEs
- PRS Administrators and investigators at UC, as well as our colleagues at other AHCs, report that they manually add organ-system to each AE entry in ClinicalTrials.gov, only because it is required in ClinicalTrials.gov. Those without access to MedDRA are choosing the organ-system for each AE using best judgment. Unless all clinical trials are required to use MedDRA as a standard vocabulary for reporting, providing the MedDRA organ-system in ClinicalTrials.gov has been and will continue to be a burden to studies not otherwise using MedDRA coding.
- The additional requirement of total number affected by organ-system will add a significant burden for investigator-initiated studies at AHCs. For example, if the organ-system field is not recorded as part of normal study conduct, it is currently added to each AE entry at the time of results reporting. The proposed requirement to summarize by organ system will require that the extra field be added to each AE in a dataset outside of ClinicalTrials.gov to be able to run a summary report (SAS, SQL) prior to data entry for results reporting. Output from such a report would then be manually entered into ClinicalTrials.gov. The data-enhancement (with organ-system) and summary report programming is a level of analytic support not currently available to investigator-initiated studies. Studies active as of the effective date, and those that are completed with results in preparation, have not budgeted for the resources needed to comply with additional programming and reporting requirements
- Industry studies do subscribe to MedDRA, and have the infrastructure, expertise, and experience to run grouping summaries; thus, this new requirement may not raise concerns from industry. This is not so for individual investigators at AHCs.

Proposed alternative(s):

- Do not require organ-system for AEs if data not used in marketing application
- Do not require organ-system for non-industry/AHC AE reporting (sponsor-investigator)



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- Do not require organ-system for non-FDA-regulated interventions
- If investigator-initiated studies at AHC's will be required to summarize AEs by organ-system in ClinicalTrials.gov, provide PRS tools to automate the summary. In other words, an option to load full-detail event-level AE data into the PRS for automatic generation of the summary to be made public.
 - Field-by-field dataset specifications for event-level AE data to upload, upon which PRS will generate the required reporting summaries: For example, date of event, subject ID, study arm, event, organ-system

General comment: *Much of the language and guidance for results reporting in ClinicalTrials.gov seems to assume that all studies have a sophisticated infrastructure, as do industry studies of FDA-regulated products. It has been difficult for individual investigators at AHCs to understand and comply with the requirements for their "Applicable Clinical Trials." Expansion of results-reporting requirements to non-drug/device studies conducted by investigators unfamiliar with ClinicalTrials.gov will create a much greater need for detailed and accessible guidance, tools, and structure to make the system understandable and navigable to individual investigators outside of industry.*

NPRM: We invite public comment on the proposed approach, experience to date with the current approach, and other information that might be collected on a voluntary basis.

Thank you for the opportunity to comment on experience to date with the current approach: Small investigator-initiated studies in academic institutions typically do not have the computing/programming/analytic support needed to generate summaries of AE data in the detail required. Experience to date includes time-intensive post-hoc sorting and manipulation of AE data in Excel to mostly-manually count frequencies. Requiring frequency by organ-system-classification will exceed our abilities to comply for investigator-initiated studies, most of which will not have adequate budget for additional programming support to apply complex summarizing and grouping logic to AE data for results reporting.

While our institution is exploring options and seeking resources to inform and support our investigators in this area, and there are many online examples of programming code that may be used for AE summaries, we request that the PRS embed a program to generate AE summary tables using an uploaded dataset formatted according to PRS specification. This would not only help small studies that do not have the budget for programming support, but also would help ensure that summaries are uniform and correct in their grouping logic.

Subpart C Results Submission § 11.48

(ii) Information for each table specified in paragraph (a)(4)(i) of this section must include the following elements:



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(E) Total Number at Risk, by Organ System.

Since the number at risk for the arm is likely to be the number at risk for each organ system, we suggest that the number at risk “by organ system” defaults to the number at risk for the entire treatment arm. Please provide examples of how a participant may not be at risk for a specific organ-system-class AE.

Subpart C Results Submission § 11.52

5. When will NIH post submitted results information? Proposed § 11.52 provides that the Director will post results information not later than 30 days after the date on which the information is submitted to the agency for an applicable clinical trial.

We are concerned that results may be posted that have not passed QA review. Suggest that language should indicate that results must pass QA review prior to public posting.

Of additional concern to investigators is whether journals / editors will continue to interpret ClinicalTrials.gov results reporting as non-publication of results given the increased results requirements. Please see below from the ICMJE website- <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>

“Will the ICMJE consider clinical trial results posted at ClinicalTrials.gov in compliance with the Food and Drug Administration Amendments Act of 2007 to be prior publication?”

It is important to note that the ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. While the ICMJE recognizes the potential problems associated with posting preliminary research results that have not yet undergone an independent peer-review process, it acknowledges that the Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII), mandates the posting of summary results data for certain trials in ClinicalTrials.gov. Thus, the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. **However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication.** The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting.”

How will investigators know if ICMJE is going to expand their requirements or if the additional requirements for results will qualify as prior-publication? A possible solution would be to comply with ClinicalTrials.gov requirements and submit results within 12 months of the last follow-up of the main outcome measure of the last participant, but withhold full public release of



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the results for up to another 12 months while papers are in pre-publication peer review and revision.

Subpart D Additional Submissions of Clinical Trial Information § 11.64

(i) If the first human subject was not enrolled in the clinical trial at the time of registration, the Study Start Date data element must be updated not later than 30 calendar days after the first human subject is enrolled.

Many investigators and IRBs often consider studies to have “started” when they are IRB-approved and recruiting, regardless of whether any participants have yet enrolled. Suggest ClinicalTrials.gov name this field “Date of First Enrolled Participant” (anticipated and actual), instead of Study Start Date.

Subpart D Additional Submissions of Clinical Trial Information § 11.64

(2) Updates to the U.S. FDA Approval, Licensure, or Clearance Status data element must be submitted not later than 15 calendar days after a change in status has occurred.

A mixture of 30-day and 15-day windows increases the complexity of understanding and complying with requirements. We strongly support that a 30-day standard window for all deadlines is more understandable and practicable; shorter windows do not seem to provide increased benefit to information seekers relative to the costs of enforcement and compliance.

Subpart D Additional Submissions of Clinical Trial Information § 11.64

(2) The Director will retain prior clinical trial registration information and clinical trial results information and make it publicly available in accordance with § 11.35 and § 11.52, respectively, through ClinicalTrials.gov so that the updates do not result in the removal of any information from the original submission or any preceding update.

NPRM: We invite public comments on our proposed approach and alternatives.

Thank you for the opportunity to comment. We think this presents the potential to confuse or mislead public who may inadvertently access incorrect information. If errors are discovered during manuscript preparation or peer-review of a manuscript, the investigator would correct any results already posted in ClinicalTrials.gov. What is the purpose of retaining and making public the incorrect information? An alternative solution would be to retain the incorrect submission, but not make it publicly available, or available only by written request, and ensure that the requestor understands that they may be receiving incorrect information.

Subpart D Additional Submissions of Clinical Trial Information § 11.66



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(a) *Correction of errors.* A responsible party who becomes aware of errors in any clinical trial information submitted under this part or is informed by NIH that such clinical trial information contains errors shall correct such errors not later than 15 calendar days after the date on which the responsible party becomes aware of the errors or on which NIH informs the responsible party of the errors, whichever is earlier.

15 days may be too short a time to post corrected results in some cases, e.g., reopen database, conduct reanalysis, internal review. Recommend additional framework to address this possibility. For example, pulling the record from public view while the sponsor tries to sort out the issue and determine if changes need to be made to the record. The difficulty and burden of compliance may be considerable, and provide little or no benefit.

II. Our General Comments about the Proposed NIH Policy and the NPRM

The proposed NIH Policy complements the NPRM in that it would apply to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the rules proposed in the NPRM.”

While we support the spirit of open access to data from any phase clinical trial, we believe the NIH’s own policy on data and safety monitoring plans for clinical research studies where the level of monitoring is commensurate with the scope of the study and safety concerns should be taken into consideration regarding ClinicalTrials.gov results reporting. Navigating the PRS to report results for small and early phase trials that do not have the budget or staff to prepare such reports will be burdensome.

Infrastructure Needed

While we support the proposed requirements for ClinicalTrials.gov registration and results reporting, it is important to keep in mind that ClinicalTrials.gov registration and specifically, results reporting are complex processes. The proposed NPRM can provide clear guidance, but successful implementation will also require IT solution for data/workflow management from NIH and the PRS system. Currently, the effectiveness and efficiency of ClinicalTrials.gov administrators at AHCs is severely hampered by the limitations of the PRS system, most notably the inability to sort, filter, or generate reports using any or all fields in the records of the institutional account. In our experience, this is one of the most complex pieces of necessary IT infrastructure that requires as careful consideration and improvement as does the implementation plan to accompany this NPRM.

Suggestions

UC’s 5 AHC’s each administer a relative high volume of ClinicalTrail.gov records. Many AHCs have similar volume. When compared to the lower volume of records managed by industry, the



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NPRM would pose a disproportionate burden on AHCs. For example, Industry AE reporting fits the proposed NPRM format whereas for AHCs it would be a significant change in reporting AEs.

The very significant burden of the proposed changes on both investigators and PRS administrators could be partially alleviated by improved communication, notification, information resources (reports, filters), and navigation in the PRS. NIH should consider an effort to improve its communications relative to PRS users, including the regularity of email reminders and problem notices. Moreover, either grandfathering trials that have already started or pushing back the implementation date or providing supplemental funds to cover the burden (OMB very conservatively estimates 41 work hours, and we believe it will be much greater) would enable better communication about and compliance with these changes.

III. Conclusion

In closing, UC agrees with the plan for an expanded registry and results data bank specified in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials.

However, in our experience, the details currently missing in the NPRM and outlined in our comments are not trivial and will require careful consideration in order to achieve the effects that NIH is looking for. To that extent, UC remains available to help shape the further details of this important NPRM initiative.

Thank you for this opportunity to comment.

Sincerely,

A handwritten signature in black ink that reads 'Wendy D Streitz'.

Wendy Streitz
Executive Director, Research Policy Analysis and Coordination

cc: Provost Dorr
Senior Vice President Stobo
Interim Vice President Tucker
Senior Vice President Peacock
Director Hall