Poster #783

The State of Infectious Diseases Clinical Trials: A Systematic Analysis of ClinicalTrials.gov

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Abstract (Modified)

Background: Evidence based medicine relies on high quality clinical research addressing areas of relevance to practicing physicians. However, there is a paucity of clinical trials informing the questions faced by Infectious Diseases specialists. Few, if any analyses have evaluated the ID clinical trials portfolio. The ClinicalTrials.gov registry offers that opportunity. It includes interventional trials of drugs, biologics, and devices mandated by the FDA Amendments Act (FDAAA) of 2007 to be registered from September 2007 in addition to other voluntarily registered studies. Recently, the Clinical Trials Transformation Initiative built a database for Aggregate Analysis of ClinicalTrials.gov and regrouped studies by clinical specialties, allowing a targeted analysis of the ID clinical trials portfolio.

Methods: In the 3-years following the FDAAA, there were 40,970 interventional trials registered with ClinicalTrials.gov. ID-related trials were identified by focusing on study conditions and interventions. Relevance to ID was manually confirmed for each potential trial yielding 3,420 ID trials and 37,550 non-ID trials for analysis.

Results: The number of ID trials is similar to the number of Cardiology (n=3,437) or Mental Health (n=3,695) trials. Treatment is the primary purpose in the majority of studies (52.3% vs. 77.0% for non-ID trials) followed by Prevention (38.6% vs. 8.3% in non-ID studies). ID trials are larger with a median enrollment size of 125 (IQR 44-400) subjects vs. 60 (IQR 30-160) for non-ID studies. Most ID studies are randomized (73.2%) but unblinded (55.8%). Industry is the funding source in 51.5% of ID studies vs. 9.9% that are NIH-funded. HIV/AIDS trials constitute the largest subset of ID trials (n=808, 23.6%), followed by Influenza Vaccine (n=375, 11.0%), and Hepatitis C (n=332, 9.7%). Compared to US and global mortality rates, HIV/AIDS and HCV trials are overrepresented whereas Lower Respiratory Tract Infection studies are under-represented in the ID clinical trials portfolio.

Conclusion: This work is the first to characterize the spectrum and nature of ID clinical trials registered in the ClinicalTrials.gov registry. It provides a framework on which to build discussions of prioritization, methodology, and policy that will in turn focus attention toward areas of greatest clinical and scientific need.

Background

Clinical trials provide information about infection prevention, diagnosis, prognosis, and treatment. However, many common questions faced by ID specialists are not addressed by evidenced-based medicine.

- >50% of recommendations contained in the Infectious Diseases Society of America (IDSA) practice guidelines are based solely upon expert opinion.
- <25% of these recommendations are based on evidence from randomized controlled trials (RCTs).[1]

The current spectrum of ID clinical trials has largely gone without systematic scrutiny regarding patterns of topical focus, geographical distribution, and levels of industry involvement. ClinicalTrials.gov, a registry of over 100,000 trials from 174 countries, provides a unique opportunity to take a "snapshot" of ID trials.

Timeline of ClinicalTrials.gov:

- **Nov 1997:** FDA Modernization Act (FDAMA) of 1997 mandated creation of the ClinicalTrials.gov registry.
- **Sept 2004:** International Committee of Medical Journal Editors' (ICMJE) established policy to require public registration of studies published in their journals (in ClinicalTrials.gov or similar registry).
- **Sept 2007:** FDA Amendments Act (FDAAA) created a legal requirement for the registration of trials of drugs, biologics, and devices with ClinicalTrials.gov.

About Clinical Trials Transformation Initiative (CTTI):[2]

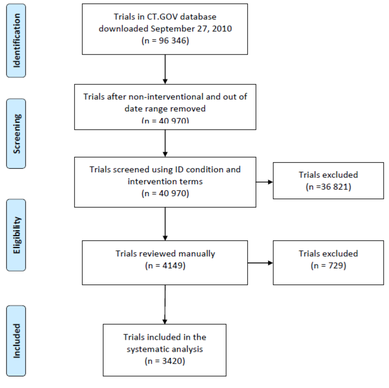
- Initiated in Nov 2007 as public-private partnership founded by FDA and Duke University and comprises >60 organizations across the clinical trials enterprise.
- Mission: identify practices that through broad adoption will increase the quality and efficiency of clinical trials.
- To improve usability of ClinicalTrials.gov, CTTI built a relational database, the Aggregate Analysis of ClinicalTrials.gov (AACT), and regrouped studies by clinical specialty.[3]

Aims of this Study:

- Characterize ID trials in ClinicalTrials.gov through a systematic analysis of characteristics of registered trials.
- Evaluate the alignment between current clinical research priorities and the infections that cause the highest morbidity and mortality in the U.S. and worldwide.

Methods

Trial Selection: 96,346 → 3,420 (see figure).



*Condition and intervention terms are defined by data submitters or linked to Medical Subject Heading (MeSH) terms generated by a National Library of Medicine (NLM) algorithm.
**Manual review performed by three ID physicians (NDG, CDP, and ELT).

Further Subcategorization and other Definitions

- ID trials were subcategorized based on study title and description. World Health Organization (WHO) cause-of-death categories were used when possible.[4]
- WHO Global Burden of Disease was used to calculate the % of ID-related mortality and disability-adjusted life years (DALY).[5]
- Probable funding source algorithm:[6]

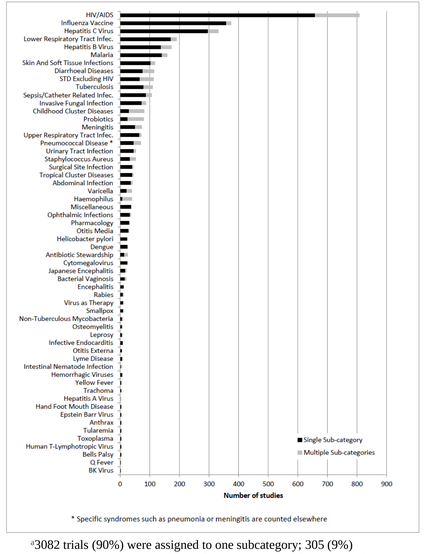
  Industry-funded: lead sponsor from industry or collaborator from industry without NIH involvement

  NIH-funded: NIH either lead sponsor or collaborator and industry not the lead sponsor.

- Descriptive statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

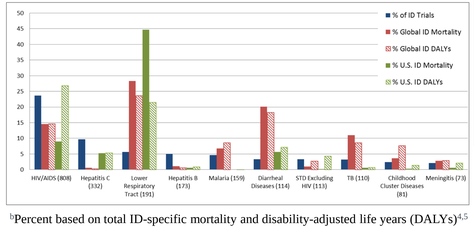
Figure 1: Distribution of ID Trials[a]



* Specific syndromes such as pneumonia or meningitis are counted elsewhere

[a]3082 trials (90%) were assigned to one subcategory; 305 (9%) assigned to two subcategories, <1% were assigned >2 subcategories.

Figure 2: ID subcategories compared to mortality and DALYs[b]



[b]Percent based on total ID-specific mortality and disability-adjusted life years (DALYs)[4,5]

Table: Characteristics of ID Trials[c]

Parameter	Non-ID	All ID	HIV/ AIDS	Hepatitis C	Malaria	Tuberculosis
Primary purpose, N	34948	3251	763	302	150	102
Treatment	26904 (77.0%)	1701 (52.3%)	473 (62.0%)	272 (90.1%)	69 (46.0%)	55 (53.9%)
Prevention	2897 (8.3%)	1255 (38.6%)	199 (26.1%)	10 (3.3%)	60 (40.0%)	27 (26.5%)
Other Purpose	5147 (14.7%)	295 (9.1%)	91 (11.9%)	20 (6.6%)	21 (14.0%)	20 (19.6%)
Type of intervention, N	37550	3420	808	332	159	110
Drug	22914 (61.0%)	1837 (53.7%)	499 (61.8%)	290 (87.3%)	107 (67.3%)	63 (57.3%)
Procedure	3976 (10.6%)	128 (3.7%)	18 (2.2%)	8 (2.4%)	5 (3.1%)	5 (4.5%)
Biological/Vaccine	1953 (5.2%)	995 (29.1%)	101 (12.5%)	35 (10.5%)	26 (16.4%)	33 (30.0%)
Behavioral	3098 (8.3%)	209 (6.1%)	150 (18.6%)	13 (3.9%)	2 (1.3%)	5 (4.5%)
Device	3706 (9.9%)	93 (2.7%)	13 (1.6%)	2 (0.6%)	7 (4.4%)	1 (0.9%)
Other intervention	6922 (18.4%)	444 (13.0%)	90 (11.1%)	26 (7.8%)	30 (18.9%)	9 (8.2%)
Vaccine	N/A	937 (27.4%)	90 (11.1%)	6 (1.8%)	24 (15.1%)	27 (24.5%)
Lead sponsor, N	37550	3420	808	332	159	110
Industry	13831 (36.8%)	1499 (43.8%)	177 (21.9%)	209 (63.0%)	25 (15.7%)	20 (18.2%)
NIH	901 (2.4%)	205 (6.0%)	111 (13.7%)	12 (3.6%)	8 (5.0%)	6 (5.5%)
U.S. Fed.	493 (1.3%)	70 (2.0%)	11 (1.4%)	6 (1.8%)	15 (9.4%)	4 (3.6%)
Govt.-For.	144 (0.4%)	81 (2.4%)	39 (4.8%)	6 (1.8%)	2 (1.3%)	7 (6.4%)
Acad./Hosp.	13102 (34.9%)	1195 (34.9%)	325 (40.2%)	80 (24.1%)	60 (37.7%)	51 (46.4%)
Consortium	205 (0.5%)	35 (1.0%)	14 (1.7%)	2 (0.6%)	1 (0.6%)	1 (0.9%)
Other	8874 (23.6%)	335 (9.8%)	131 (16.2%)	17 (5.1%)	48 (30.2%)	21 (19.1%)
Funding source, N	37550	3420	808	332	159	110
Industry	17074 (45.5%)	1763 (51.5%)	291 (36.0%)	227 (68.4%)	31 (19.5%)	30 (27.3%)
NIH	3198 (8.5%)	340 (9.9%)	189 (23.4%)	17 (5.1%)	16 (10.1%)	12 (10.9%)
Other	17278 (46.0%)	1317 (38.5%)	328 (40.6%)	88 (26.5%)	112 (70.4%)	68 (61.8%)
Masking/Blinding, N	36479	3392	801	327	157	110
Open	20340 (55.8%)	1894 (55.8%)	543 (67.8%)	200 (61.2%)	120 (76.4%)	74 (67.3%)
Single Blind	4156 (11.4%)	301 (8.9%)	63 (7.9%)	7 (2.1%)	7 (4.5%)	3 (2.7%)
Double Blind	11983 (32.8%)	1197 (35.3%)	195 (24.3%)	120 (36.7%)	30 (19.1%)	33 (30.0%)
Allocation, N	35885	3355	790	321	151	108
Randomized	24570 (68.5%)	2457 (73.2%)	565 (71.5%)	220 (68.5%)	110 (72.8%)	72 (66.7%)
Non-Randomized	11315 (31.5%)	898 (26.8%)	225 (28.5%)	101 (31.5%)	41 (27.2%)	36 (33.3%)
Enrolment, N	36987	3379	797	328	153	110
Median (IQR)	60 (30, 160)	125 (44, 400)	65 (30, 240)	60 (30, 148)	261 (48, 1050)	81 (36, 250)
Regional distribution, N	34425	3095	736	268	153	104
Africa	527 (1.5%)	290 (9.4%)	118 (16.0%)	4 (1.5%)	87 (56.9%)	37 (35.6%)
Central America	346 (1.0%)	110 (3.6%)	33 (4.5%)	33 (12.3%)	0 (0%)	0 (0%)
Eastern Asia	3249 (9.4%)	286 (9.2%)	18 (2.4%)	40 (14.9%)	1 (0.7%)	10 (9.6%)
Europe	10417 (30.3%)	894 (28.9%)	176 (23.9%)	90 (33.6%)	15 (9.8%)	28 (26.9%)
Middle East	1458 (4.2%)	87 (2.8%)	3 (0.4%)	18 (6.7%)	0 (0%)	3 (2.9%)
North America	20173 (58.6%)	1408 (45.5%)	408 (55.4%)	147 (54.9%)	19 (12.4%)	18 (17.3%)
North Asia	782 (2.3%)	47 (1.5%)	11 (1.5%)	1 (0.4%)	0 (0%)	5 (4.8%)
Pacifica	985 (2.9%)	102 (3.3%)	15 (2.0%)	23 (8.6%)	3 (2.0%)	1 (1.0%)
South America	1329 (3.9%)	186 (6.0%)	41 (5.6%)	18 (6.7%)	8 (5.2%)	8 (7.7%)
South Asia	759 (2.2%)	117 (3.8%)	11 (1.5%)	3 (1.1%)	7 (4.6%)	8 (7.7%)
Southeast Asia	706 (2.1%)	140 (4.5%)	43 (5.8%)	2 (0.7%)	16 (10.5%)	9 (8.7%)
Unknown	3125 / 37750 (8.3%)	325/ 3420 (9.5%)	72 /808 (8.9%)	64 /332 (19.3%)	6 /159 (3.8%)	6 /110 (5.5%)

[c]Numbers in light gray boxes indicate the # of trials providing data for the specified parameter
N/A= Not Available

Conclusions

- ID trials are well represented in the overall clinical trials enterprise, tend to be larger than non-ID trials, and have a greater representation outside the U.S. than do other specialties.
- There are discrepancies between the number and quality of ID trials in some disease states relative to the burden of disease
- This "snapshot" of ID trials should prompt examination of how best to prioritize and coordinate future ID clinical research priorities.

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Disclosures

None of the authors has any conflicts of interest to declare.