Characteristics and data reporting of rare disease clinical trials: Getting better but still room for improvement

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ABSTRACT

Background

It is estimated that there are more than 7,000 rare diseases (RDs) worldwide, impacting the lives of approximately 400 million people and only 5% have an approved therapy. Facing special challenges, including patient scarceness, incomplete knowledge of the natural history and only few specialized clinical sites, clinical trials (CT) are limited, making the data from trials critical for research and clinical care. Despite the introduction of the U.S. Food and Drug Administration Amendment Act (FDAAA) in 2007 requiring certain CTs to post results on the registry ClinicalTrials.gov within 12 months following completion, compliance has been reportedly poor. Here, we describe general characteristics of RD CTs, identify trends, and evaluate result reporting practices under the FDAAA aiming to draw awareness to the problem of non-compliance.

Methods

CTs conducted between 2008 and 2015 were extracted from the public U.S. trial registry ClinicalTrials.gov using the text mining software I2E (Linguamatics). Disease names were matched with rare disease names from the Orphanet Rare Disease Ontology (ORDO, v2.5, Orphanet). Statistical analyses and data visualization were performed using GraphPad Prism 7 and R (v3.5). The Student's t-test was employed to calculate significance using p-value cut-offs of <0.05 or <0.001.

Results

We analyzed 1,056 RD CTs of which 55.7% were phase 2, 7.7% phase 2/3 and 36.7% phase 3 trials. The studies were mostly one- and two-armed experimental CTs with the majority (60.2%) being funded by industry. Cystic fibrosis and sickle cell disease represented the most frequently investigated diseases (25.0% and 16.5%). Industry-led phase 2 RD CTs were significantly ($p<0.0001$) shorter than their equivalent led by academia/non-profit (22 vs. 33

months). Screening CTs completed before the end of 2015, we found that of the 725 analyzed studies, 55.2% predominantly phase 2 CTs, did not report results. Taking their potential applicability to the FDAAA into account, 25.2% industry-funded and 28.0% academia/non-profit-funded trials failed to disclose results on ClinicalTrial.gov.

Conclusion

RD CTs tend to be comparatively small, industry-funded studies focusing on genetic and neurologic conditions. Sponsor-related differences in study design, duration, and enrollment were observed. There are still substantial shortcomings when it comes to result publication.

Key words: ClinicalTrials.gov, rare disease, result publication, FDAAA

INTRODUCTION

In the U.S., rare diseases (RDs) are defined as affecting less than a total of 200,000 people, in Europe the definition is based on a frequency of 1 in 2,000 or fewer people. It is estimated that there are more than 7,000 RDs which together impact the lives of approximately 400 million people worldwide[1], with only half of them being genetically characterized[2]. The medical need is still high as only 5% of RDs currently have an approved therapy[3]. In order to foster research in these largely underserved orphan diseases, the U.S. Food and Drug Administration (FDA) introduced the Orphan Drug Act in 1983 providing various incentives for the development of treatments[4]. Despite this initiative being very successful with 745 FDA approvals (428 in the last ten years), 99.9% of which filed by industry, more therapies are needed[5].

Clinical research in RDs faces challenges which usually have less impact on clinical trials (CTs) conducted in common diseases. These include patient scarceness, incomplete knowledge of the natural history and limited clinical sites able to treat these patients. This often results in a limited number of CTs in each RD, making the data from trials critical for research and clinical care. Despite the introduction of the U.S. Food and Drug Administration Amendment

Act (FDAAA) in 2007[6] requiring CTs matching specific criteria to post results on ClinicalTrials.gov within 12 months following trial completion, compliance has been reportedly poor, which may directly impact patient care and therapy development [7–9]. The purpose of this report is to describe the general landscape of rare disease clinical trials (RD CTs), identify trends, and also evaluate result reporting practices after the introduction of the FDAAA with the goal of drawing awareness to the problem of non-compliance.

METHODS

Data sources

Trial records with a clinical trial identifier (NCT number), a brief/official title and a study start and end date between 2008 and 2015 were extracted from the publicly accessible U.S. trial registry ClinicalTrials.gov using the text mining software I2E from Linguamatics. The glossary of common site terms, which can be found on ClinicalTrials.gov[10], was used to determine if a CT was experimental, interventional, used an active comparator and other terms used in this paper.

Data set development

In order to distinguish RD CTs from common disease CTs, ClinicalTrials.gov condition specifications were matched with RD names from the Orphanet Rare Disease Ontology (ORDO) version 2.5 provided by Orphanet. Trials studying (rare) malignancies and communicable diseases were excluded, as well as all studies in phases 1, 1/2 and 4, and those without a study phase. Oncology CTs were excluded as rare oncology diseases are often included amongst other more common cancers as part of basket trials and thus did not reflect a RD CT. Infectious disease CTs included many HIV and hepatitis studies, which are not rare

101 in much of the world and thus were excluded. Phase 1 studies comprise healthy subjects, not
102 reflecting RD patient populations.
103 Studies starting before 2008 were excluded, due to the introduction of the FDAAA in 2007, as
104 well as studies with a study status other than "completed". Finally, studies involving incorrectly
105 entered information into the "condition" field of the registry or studies that involved poisoning
106 or envenomations were manually removed. To examine result reporting, we generated a second
107 data set including studies with an indicated completion date beyond 2015, to provide the
108 responsible party with more than two years for the study results to be analyzed and entered on
109 ClinicalTrials.gov at the time of our analysis.
110 To determine study location, all study locations in the contacts and locations section of each
111 study's ClinicalTrials.gov record were examined and counted. A site was counted every time
112 it was mentioned by a CT. Therefore, a single study site was included multiple times if it hosted
113 more than one CT during the time period examined.
114 To determine the sponsor, we extracted the responsible party as indicated on ClinicalTrials.gov
115 and manually allocated CTs to "industry" or "academia/non-profit" according to the source of
116 funding. "Industry" referred almost exclusively to registered for-profit companies, while
117 publicly funded entities, such as universities, foundations, associations and non-profit
118 organizations were allocated to "academia/non-profit". One study in the final data set of 1,056
119 studies could not be unambiguously allocated to a sponsor and was therefore excluded from
120 the respective analyses.
121
122 **Statistical analyses and data visualization**
123 Statistical analyses and data visualization were performed using GraphPad Prism 7. Microsoft
124 Excel was used for statistical calculations to analyze enrollment due to cell number limitations

125 in GraphPad Prism 7. For calculations of significance, Student's t-test was employed using p-
126 value cut-offs of <0.05 or <0.001 to demonstrate significant results.
127
128 **RESULTS**
129 **Design characteristics of rare disease clinical trials (RD CTs)**
130 An overview of the workflow resulting in the final data set comprising 1,056 RD CTs is shown
131 in **Fig 1**. Examining the general characteristics of the studies (**Table 1**), we found that trials
132 were equally distributed across all years from 2008 to 2015 (12.5 ± 1.8% trials per year). More
133 than half of the studies analyzed were in phase 2 (55.7%), followed phase 3 (36.7%) and 2/3
134 (7.7%). While phase 2 and phase 3 CTs showed a similar proportion of experimental (77.9%
135 and 75.5%) and active comparator (17.3% and 21.7%) study arm types, phase 2/3 CTs tended
136 to include more active comparator studies (29.6%) with 67.9% of the studies being
137 experimental. Here, 49.4% of all CTs are two-armed studies, followed by one-armed studies
138 (31.7%). A total of 60.2% CTs were industry-funded and 39.8% were academia/non-profit-
139 funded. While phase 2 and phase 3 CTs were predominantly industry-sponsored, with 53.9%
140 and 74.1%, respectively, academia/non-profit prevailed in phase 2/3 CTs (60.5%).
141

Study Start Year	**n (%)**
2008	149 (14.1)
2009	138 (13.1)
2010	137 (13.0)
2011	146 (13.8)
2012	144 (13.6)
2013	130 (12.3)
2014	120 (11.4)
2015	92 (8.7)
Study Arm Type	**n (%)**
Phase 2	**588 (55.7)**

Study Phases	**n (%)**
Phase 2	588 (55.7)
Phase 2/3	81 (7.7)
Phase 3	387 (36.7)
Number of Arms	**n (%)**
Phase 2	**588 (55.7)**
1	200 (18.9)
2	256 (24.2)
3	76 (7.2)
4	39 (3.7)
5	10 (0.9)

Active Comparator	102 (9.7)	6	3 (0.3)
Experimental	458 (43.4)	8	1 (0.1)
No Intervention	1 (0.1)	10	1 (0.1)
Other	14 (1.3)	22	1 (0.1)
N/A	13 (1.2)	N/A	1 (0.1)
Phase 2/Phase 3	**81 (7.7)**	**Phase 2/3**	**81 (7.7)**
Active Comparator	24 (2.3)	1	19 (1.8)
Experimental	55 (5.2)	2	50 (4.7)
Other	1 (0.1)	3	7 (0.7)
Placebo Comparator	1 (0.1)	4	5 (0.5)
Phase 3	**387 (36.6)**	**Phase 3**	**387 (36.7)**
Active Comparator	84 (8.0)	1	116 (11.0)
Experimental	292 (27.7)	2	215 (20.4)
Other	8 (0.8)	3	37 (3.5)
Placebo Comparator	1 (0.1)	4	12 (1.1)
N/A	2 (0.2)	5	2 (0.2)
		6	4 (0.4)
		7	1 (0.1)

Table 1. *Characteristics of the 1056 completed Phase 2, 2/3 and 3 CTs registered at ClinicalTrials.gov. For each study arm type, the overall distribution of the evaluated CTs is highlighted in bold with the respective proportion of each study arm type listed below. The same applies to the table depicting the number of study arms.*

Disease categories

To generate a more comprehensive view of the RD CT landscape, we analyzed the disease areas addressed in this data set. By leveraging the Orphanet Diseases 2.5 ontology, we were able to map all but one trial to specific conditions. Each CT could be allocated to up to seven diseases and each disease could be assigned to more than one category. The ten most common rare disease categories were genetic disease (19.4%), neurologic disease (12.3%), respiratory disease (8.2%), eye disease (6.4%), systemic or rheumatologic disease (5.9%), hematologic

154 disease (5.4%), renal disease (5.0%), infertility (4.7%), skin disease (4.4%) and developmental
155 defect (4.1%). These accounted for a total of 75.8% of all diseases. In fact, 92.9% (n=971) of
156 the RD CTs were mapped to at least one of the top 10 categories. In detail, 35.8% (n=378) of
157 the studies were mapped to one top-ten category, 21.8% (n=230) were mapped to two and
158 20.5% (n=216) to three.
159 Furthermore, we found that the top ten diseases account for 86.2% of all CTs with cystic
160 fibrosis (CF) accounting for 25.0%, followed by sickle cell disease (16.5%), hemophilia
161 (8.7%), Fabry disease (6.3%), fragile X syndrome (6.1%), Huntington disease (5.7%),
162 sarcoidosis (4.9%), systemic sclerosis (4.9%), Friedreich Ataxia (4.3%) and muscular
163 dystrophies (primarily Duchenne, but also Becker and oculopharyngeal muscular dystrophy)
164 (3.9%). To determine whether the ten most investigated diseases also reflect the leading
165 diseases in each category, the various conditions were analyzed based on their by the sponsor
166 designated category. While, CF dominates the "rare" categories genetic diseases (15.7%),
167 respiratory diseases (37.1%) and infertility (64.2%), sickle cell disease was found first in the
168 categories systemic or rheumatologic disease (16.9%) and renal disease (20.0%). The three
169 most researched conditions in other areas are hemophilia (29.3%) in hematologic disease,
170 alopecia (24.2%) in skin disease, and amyotrophic lateral sclerosis (12.1%) in neurologic
171 disease.
172 Compared to the entire corpus of 2,257,370 CTs entered in ClinicalTrials.gov, most studies in
173 ClinicalTrials.gov investigated cancers and other neoplasms (13.8%), followed by general
174 pathology (10.5%), nervous system diseases (9.2%), digestive system diseases (6.7%), heart
175 and blood diseases (6.6%) and behaviors and mental disorders (6.5%). Thus, RD CTs represent
176 a different spectrum of disease areas as compared to more common diseases. To summarize,
177 the majority of the investigated diseases in our data set are rare genetic and neurologic
178 conditions with the most extensively explored conditions being CF and sickle cell disease.

179

180 **Intervention type**

181 Next, intervention types across study phases together with sponsors were analyzed (**Table 2**).
182 Compared to ClinicalTrials.gov, where 45.6% (n=135,555) of all registered CTs involve drugs
183 and biologicals as primary intervention type[11], drug interventions (including small molecules)
184 constituted 78.5% (n=829) of the CTs in our data set, followed by biologicals (13.1%, n=138).
185 In detail, 81.3% (n=257) of phase 2 RD CTs conducted by industry were found to involve
186 drugs, followed by biologicals (14.2%, n=45) and devices (2.2%, n=7). Similarly, drugs and
187 biologicals with 78.7% (n=214) and 5.9% (n=16) respectively, made up the majority of phase
188 2 CTs in the academia/non-profit sector. Notably, academia/non-profit-led trials tended to
189 investigate intervention types beyond drugs or biologicals, such as dietary supplements,
190 devices or procedures. Phase 3 RD CTs were found to be almost exclusively industry-
191 sponsored and investigate drugs (78.4%) or biologicals (20.9%). Academia/non-profit CTs
192 focused on drugs (79.8%), but not on biologicals (1.0%). In summary, the majority of studies
193 investigate drugs with the main sponsor being industry, whereas academia/non-profit-led trials
194 tend to explore a broader range of intervention types.

195

	Industry			**Academia/Non-Profit**		
Intervention Type per phase	**n (% per Phase)**	**n (% per Intervention Type)**	**n of CTs in this phase (%)**	**n (% per Phase)**	**n (% per Intervention Type)**	**n of CTs in this phase (%)**
Phase 2	**316 (53.7)**			**272 (46.3)**		
Behavioral	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	5 (100.0)	5 (1.8)
Biological	45 (7.7)	45 (73.8)	45 (14.2)	16 (2.7)	16 (26.2)	16 (5.9)
Combination Product	1 (0.2)	1 (100.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Device	7 (1.2)	7 (53.8)	7 (2.2)	6 (1.0)	6 (46.2)	6 (2.2)
Dietary Supplement	1 (0.2)	1 (11.1)	1 (0.3)	8 (1.4)	8 (88.9)	8 (2.9)
Drug	257 (43.7)	257 (54.6)	257 (81.3)	214 (36.4)	214 (45.4)	214 (78.7)
Genetic	1 (0.2)	1 (50.0)	1 (0.3)	1 (0.2)	1 (50.0)	1 (0.4)

Other	1 (0.2)	1 (11.1)	1 (0.3)	8 (1.4)	8 (88.9)	8 (2.9)
Procedure	3 (0.5)	3 (20.0)	3 (0.9)	12 (2.0)	12 (80.0)	12 (4.4)
Radiation	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (100.0)	2 (0.7)
Phase 2/Phase 3	**32 (39.5)**			**49 (60.5)**		
Behavioral	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (100.0)	1 (2.0)
Biological	14 (17.3)	14 (87.5)	14 (43.8)	2 (2.5)	2 (12.5)	2 (4.1)
Device	1 (1.2)	1 (25.0)	1 (3.1)	3 (3.7)	3 (75.0)	3 (6.1)
Dietary Supplement	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.9)	4 (100.0)	4 (8.2)
Drug	16 (19.8)	16 (30.2)	16 (50.0)	37 (45.7)	37 (69.8)	37 (75.5)
Other	1 (1.2)	1 (100.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Procedure	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	2 (100.0)	2 (4.1)
Phase 3	**287 (74.4)***			**99 (25.6)***		
Behavioral	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (100.0)	2 (2.0)
Biological	60 (15.5)	60 (98.4)	60 (20.9)	1 (0.3)	1 (1.6)	1 (1.0)
Device	1 (0.3)	1 (25.0)	1 (0.3)	3 (0.8)	3 (75.0)	3 (3.0)
Dietary Supplement	1 (0.3)	1 (16.7)	1 (0.3)	5 (1.3)	5 (83.3)	5 (5.1)
Drug	225 (58.3)	225 (74.0)	225 (78.4)	79 (20.5)	79 (26.0)	79 (79.8)
Other	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	5 (100.0)	5 (5.1)
Procedure	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	4 (100.0)	4 (4.0)

Table 2. *Intervention Type per Phase and Sponsor for 1055 completed phase 2, 2/3 and 3 CTs registered at ClinicalTrials.gov. One study was removed from the analysis since the sponsor could not be assigned unambiguously to any of the two categories.*

Study location

The selection of investigational sites can be pivotal for enrollment and overall study success and their number varies considerably depending on the sponsor. Out of the 1,056 trials in our data set, 632 (59.8%) entered at least one study site and, analyzing both sponsor categories separately, no significant difference was found. While 58.3% of all 635 CTs run by industry entered a study location, it was 62.1% of those run by academia/non-profit out of a total of 420. One study could not be allocated to a sponsor and was therefore excluded leaving 1,055 trials

208 for analysis. Although CTs from all around the world can be registered in ClinicalTrials.gov,
209 we found that 44.3% (n=4,431) of the study sites were located in the U.S.. Here, the sum of
210 counts by location does not equal the total CT number, as each location indicated by a study is
211 counted and a single study may be counted more than once. Analyzing the number of sites by
212 continent, the majority of sites are located in North America (48.5%, n=4,845) and Europe
213 (33.9%, n=3,387), followed by Asia (11.4%, n=1,141), Central and South America (2.9%,
214 n=286), Australia and Oceania (2.7%, n=269) and Africa (0.7%, n=72). The countries with the
215 most study sites were the U.S. with 4,431 sites, Germany with 621 sites, France with 566 sites,
216 Japan with 429 sites, Canada with 414 sites and the UK with 395 sites as well as Italy and
217 Spain, with 326 and 251 sites, respectively. Approximately one third of RD CTs were run at a
218 single site (34.7%, n=219), followed by 14.9% with up to five sites, 12.5% with up to ten sites
219 and 9.7% with up to 15 sites. 4.6% and 5.4% of the studies had up to 15 and 25 study sites,
220 respectively, and 1.6% indicated more than 100. The remaining 16.8% were scattered between
221 25 and 100 study sites. Moreover, industry-led trials significantly increased the number of
222 study sites with ascending study phase. Accordingly, the mean location number for industry in
223 phases 2, 2/3 and 3 was 15.0 (median of 7.5), 23.0 (median of 18.0) and 32.7 (median of 23.5),
224 while for academia the location numbers per phase were 3.1 (median of 1.0), 4.6 (median of
225 1.0) and 9.6 (median of 1.0). Compared to the entire trial corpus present on ClinicalTrials.gov,
226 where 40% of the CTs indicated trial sites in the U.S. (35% U.S. only and 5% U.S. and non-
227 U.S.), we found that RD CTs tend to be more often conducted in the U.S. (44.3%). In summary,
228 the vast majority of trials entered in ClinicalTrials.gov are conducted in North America and
229 Europe and despite a correlation between higher numbers of study centers and industry
230 funding, studies run at only one site are the most common.
231
232 **Participant enrollment**

233 CT patient recruitment is critical and can be especially challenging in RD CTs due to patient
234 scarceness and dispersion. The enrollment numbers in our data set follow the typical trend
235 observed in common diseases in that the number of participants increases with progressing
236 study phase. Participant numbers were heterogeneous, as reflected by considerable standard
237 deviation values. The median patient recruitment for industry CTs in phases 2, 2/3 and 3 was
238 40.0 (interquartile range (IQR), 21-76), 77.5 (IQR, 50-227), and 80.5 (IQR, 37-191),
239 respectively, vs. 26.0 (IQR, 12-47), 35.0 (IQR, 20-88) and 60.0 (IQR, 23-110) for
240 academia/non-profit CTs. This enrollment difference between sponsor types was significant
241 ($p<0.05$) in phases 2 and 2/3. The mean enrollment was approximately 96% (industry) and 83%
242 (academia/non-profit) higher than the median. Of the 73,071 participants enrolled in industry-
243 funded trials, 59.4% had been recruited for phase 3 CTs, followed by 33.6% for phase 2 CTs,
244 and 6.9% for phase 2/3 CTs. Academia/non-profit enrolled 44.0% of a total of 24,959
245 participants in phase 3 CTs, 40.7% in phase 2 CTs, and 15.3% in phase 2/3 CTs. Analyzing
246 gender eligibility in RD CTs we found that the majority of the studies, 89.3%, admitted
247 participants of any sex, while 7.1% and 3.6% of RD CTs enrolled only male or female subjects,
248 respectively. In summary, industry-led trials in all phases enrolled consistently more patients
249 than academia/non-profit-funded trials, with notable variability as reflected by the standard
250 deviation in enrollment.
251

252 **Participant Age**

253 A RD can affect anyone irrespective of age, but at least half of RDs manifest themselves in
254 early childhood. To determine if this is reflected in RD CTs, the participant age was assessed.
255 Therefore, the entries for the ClinicalTrials.gov categories “participant age”, “participant
256 minimum age” and “participant maximum age” were retrieved and summarized in **Table 3**. A
257 minimum age for participants was entered for 92.9% (n=981). Of the CTs showing a minimum

258 age, 88.2% allowed patients under 18 years to be enrolled. In contrast, only 56.3% of the studies
259 indicated an upper age limit for participants. Of those, 41.6% indicated an extended age of
260 eligibility above 65 years and a notable fraction (15.2%) of trials set the maximum age between
261 11 and 18 years. While extracting the minimum and maximum age limits was fairly
262 straightforward, the analysis of the participant age, filled out by 96.8% of the studies, proved
263 complicated due to the lack of uniformity of the information entered. After manual
264 categorization into age groups, we were able to visualize the data (**Fig. 2**). Even though around
265 three quarters of the studies set the upper age limit to more than 60 years, numerous studies put
266 their focus on a younger population, mirrored by the high proportion of studies indicating a
267 minimum participant age below 18.

268

Participant Minimum Age	n (%)	Participant Maximum Age	n (%)
< 1 year	24 (2.5)	< 1 year	15 (2.5)
1-10 years	204 (20.8)	1-10 years	31 (5.2)
11-18 years	637 (64.9)	11-18 years	90 (15.2)
19-35 years	66 (6.7)	19-35 years	47 (7.9)
36-65 years	50 (5.1)	36-65 years	164 (27.6)
65<	0 (0.0)	65<	247 (41.6)
Total	**981 (100)**	**Total**	**594 (100)**

269 ***Table 3.*** *Participant minimum and maximum age as indicated by RD CTs in our data set (n=1056).*

270

271 **Study duration**

272 Another aspect of CTs is study duration, as calculated in this analysis from the study start to
273 the study completion date. We found that phase 2 studies conducted by industry were, with a
274 median duration of 22 months (IQR, 14-33), significantly ($p<0.0001$) shorter than their
275 academia/non-profit-led equivalent, with a median duration of 33 months (IQR, 22-47)(**Fig.**
276 **3**). This trend could be similarly observed in phase 3 CTs, with industry conducting shorter

277 studies with a median of 27 months (IQR, 18-41) versus 34.5 months (IQR, 19-52) for
278 academia/non-profit CTs ($p<0.05$). In contrast, the study duration did not differ significantly
279 in phase 2/3 CTs between industry and academia/non-profit with a median of 29 (IQR, 21-37)
280 and 31 (IQR, 18-48), respectively. In summary, industry-funded phase 2 and 3 RD CTs are of
281 a shorter duration than studies led by academia/non-profit.
282
283 **Result reporting among rare disease clinical trials**
284 In 2007, the FDAAA was introduced requiring the posting of results for eligible studies on
285 ClinicalTrials.gov within twelve months after study completion (FDAAA section 801). A CT
286 qualifies as eligible or applicable to the FDAAA if the drug, biological or device under
287 investigation has been manufactured in the U.S. or its territories, or if the CT has at least one
288 study site in the U.S. or its territories. To examine result reporting, a second data set of (n=725
289 CTs) consisting of 55.9% phase 2, 7.6% phase 2/3, and 36.6% phase 3 CTs was generated
290 (further information provided in **Supplementary table 1**). Overall, 44.8% (n=325) trials had
291 entered results while 55.2% (n=400) had not. Of those that failed to report results, 65.8% were
292 phase 2, 9.8% were phase 2/3, and 24.5% were phase 3 CTs. Industry reported consistently
293 more results over all years (2008-2015) with a total of 56.3% (n=243) reporting RD CTs.
294 Strikingly, only 28.0% (n=82) of studies conducted by academia/non-profit did likewise. To
295 explore if sponsors in the non-reporting data set were meeting their obligations under the
296 regulations, we extracted the RD CTs which were identified as including at least one U.S. site
297 (n=134) or using a drug manufactured within the U.S. (n=1). For the remainder of the studies
298 (n=265) determining if the FDAAA was applicable could not be easily concluded from the
299 information included in ClinicalTrials.gov, thus a random sample of approximately 25%
300 (n=67) were examined manually. The majority (n=53, 79.1%) of the studies in this sample were
301 not applicable to the FDAAA, while four (6%) CTs were identified as applicable. The

302 remaining ten (14.9%) studies in this sample did not provide enough information for a clear
303 categorization. We found that one of the studies that was not applicable displayed the status
304 "results submitted" with no results entered in the respective entry field meaning that the results
305 might currently be under evaluation. Extrapolating the manually extracted data set of 67 studies
306 to the results of the overall number of non-reporting trials, we estimated that 20.8% of the
307 included 725 CTs failed to report results although required by U.S. law. Thereof, 105 CTs
308 (24.3%) are industry-funded and 46 CTs (15.7%) academia/non-profit-funded studies. Adding
309 trials with unclear applicability (0.9% industry- and 12.3% academia/non-profit-led CTs), the
310 overall proportion of result non-reporting CTs, although (potentially) legally required,
311 increases to 25.2% and 28.0% for studies initiated by industry and academia/non-profit,
312 respectively. In summary, more than half of the industry-funded and roughly one third of
313 academia/non-profit-funded RD CTs report results online after study completion. Of those that
314 unambiguously fall under the regulation of the FDAAA, CTs sponsored by academia/non-
315 profit enter results more often than industry-led CTs, with the latter posting more results online
316 on a voluntary basis. However, including also potentially applicable CTs, result reporting
317 practices do not differ between sponsors.
318

319 **DISCUSSION**

320 We conducted a landscape analysis of completed phase 2, 2/3 and 3 RD CTs registered in the
321 ClinicalTrials.gov database, including CTs from all disease areas except oncology and
322 infectious diseases. RD CTs were shown to be mostly sponsored by industry, which is in line
323 with previous findings in more common diseases[12]. Academia/non-profit CTs prevail in phase
324 2/3 possibly because CTs in this phase often explore already approved drugs in new
325 populations, or for extended indications. This falls in line with a previous observation of
326 academia-led trials peaking predominantly before phase 3[13]. The present industry dominance

327 in phase 3 CTs, which often are needed for regulatory approval, can be linked to those trials
328 characteristically being large and of longer duration rendering them costly. Similar to previous
329 reports, drug interventions represent the most frequent type of intervention in our data set[14].
330 Unsurprisingly, industry focused on drugs and biologicals in all phases, with biologicals more
331 common in phase 2/3. Academia/non-profit, although similarly focused on drugs, explored a
332 broader array of interventions, including devices and dietary supplements. That might be
333 partially due to the challenges posed by the nature and diversity of the dietary supplements
334 branch and its globally varying regulations among different jurisdictions or governmental
335 dominance in this field[15]. The strong presence of academia/non-profit sponsors in CTs around
336 biologicals and drugs could be due to research done on approved drugs aiming to extend their
337 scope towards new applications or patient groups in RDs. As previously reviewed[16],
338 pharmaceutical companies and academics are entering into collaborations to repurpose
339 approved or discontinued drugs for other indications, including RDs. This may explain the
340 increased numbers of non-industry sponsored phase 2/3 trials. Overall, comparing our data with
341 similar data in ClinicalTrials.gov, no differences between our RD data set and the CTs in more
342 common diseases could be detected and intervention types employed in RD research, with the
343 largest group being phase 2 CTs investigating drugs conducted by industry, reflect the common
344 practice in general clinical research[17].
345 Most RD CTs are genetic or neurologic diseases. The high prevalence of genetic CTs in the
346 RD data set is to be expected, as the majority of RDs are thought to be genetic in origin[18].
347 Among these, CF is the most researched disease, representing also the most common genetic
348 disease in Caucasian children counting 70,000 cases worldwide. This substantial number of
349 patients, paired with early screening policies and a molecular understanding of the disease
350 facilitates the setup of CT and thereby therapy development[19-20], leading pharmaceutical
351 companies to conduct studies in this field[21]. Similar reasons might apply for neurologic

352 disorders, the second focus of CTs in our data set, which occur relatively frequently in the
353 pediatric population[22]. These observations are in line with what can be found for common
354 diseases present in ClinicalTrials.gov, where nervous system disorders are the most researched
355 disease area, followed by neoplasms and general pathologies. In contrast, digestive system
356 diseases, heart and blood diseases, and behaviors and mental disorders were highly represented
357 in ClinicalTrials.gov, but not in our RD data set. Therefore, although rare diseases are
358 numerous, the vast majority of clinical trials focus on a few disease categories and conditions,
359 such as CF. Furthermore, we found Huntington disease (HD) representing the top disease in
360 rare eye disorders, followed by uveitis. Although HD is not primarily an eye disorder, a
361 possible explanation for this finding could be a common endpoint in this disease (Unified
362 Huntington's Disease Rating Scale), including ocular assessments causing its misclassification
363 as eye disorder. This example highlights the difficulties that can occur when analyzing data
364 from Clinicaltrials.gov that has not been curated or reviewed critically.
365 In line with a recently published study[23], we identified North America and Europe as the
366 regions and the U.S. and Germany as the countries with the most study locations. The high
367 proportion of U.S.-led CTs could be explained by the strong presence of the pharma industry
368 compared to other countries with the ensuing availability of financial and infrastructural
369 resources as well as the strong presence of active patient associations and foundations that play
370 a key role in advancing research[21]. Japan, Australia, Argentina and South Africa were the
371 countries with most CTs in Asia, the Oceania region, Middle and South America and Africa,
372 respectively. However, 40.2% of CTs did not report a location, biasing the data and its
373 interpretation. In accordance with a previous report analyzing the International Clinical Trial
374 Registry Platform (ICTRP), we found Japan to be the country with the most CT sites in Asia[23].
375 While the mentioned report attributes the shift away from "traditional" CT sites in Western
376 countries to lower study costs in other countries, the study location for RD CTs could be more

377 influenced by patient prevalence, the availability of specialized care centers and specific
378 legislation fostering RD research[24-25].
379 Considering the general scarceness of patients and experts/specialized care centers in RDs, it
380 is not surprising that half of the trials indicate at most five sites. In contrast, almost two thirds
381 of the trials indicated more than one study site, pointing towards the implementation of more,
382 but smaller study sites in RD research. Support for this hypothesis might be provided by Bell
383 and Smith et *al.* who, looking at interventional CTs, found that RD CTs have less study sites
384 compared to non-RDs[26]. The correlation we found between industry-funded CTs and an
385 increased number of study sites could be linked to the different financial support received
386 compared to academia/non-profit.
387 Although phase 2 CTs prevail in our data set, most participants were enrolled in phase 3 CTs,
388 with the majority enrolled in industry sponsored CTs. A study analyzing common disease CTs
389 of all phases reported an overall enrollment rate below 100 participants for 62% of studies,
390 which was the same percentage we observed in phase 3 CTs in ClinicalTrials.gov. Examining
391 phase 2 and 2/3 RD CTs, the proportion of studies enrolling 100 or less patients rose to 87.8%
392 and 72.8%, respectively. Comparing our data set to the aforementioned study based on the
393 respective median enrollment, we found comparable accrual numbers between RD CTs overall
394 and therein described oncology trials, whilst mental health and cardiovascular CTs were higher
395 at 85 and 100, respectively. It is somewhat surprising that the number of patients in RD CTs
396 and non-RD CTs are similar, as we expected RD CTs to enroll fewer patients as previously
397 indicated in a study comparing rare with non-rare disease CTs[26]. While this study describes
398 mostly early phase CTs with fewer participants, most of the patients in our data set were
399 enrolled in phase 3 CTs. Additionally, the limited power of small studies to show significant
400 clinical efficacy, might be avoided by study sponsors resulting in higher accrual numbers.
401 Reasons for less participant accrual in non-RD CTs could be competing trials targeting similar

402 participant populations or even an increased focus on small sub-populations within a larger
403 disease area. This indicates that CTs in RDs and more common diseases may be becoming
404 more similar and both may have issues with recruitment of sufficient numbers of patients to
405 draw firm conclusions. Notably, we observed great heterogeneity between trials enrolling few
406 patients, sometimes in single digits and trials enrolling hundreds or thousands, a phenomenon
407 that has also been previously reported[17].
408 Gender disparity in biomedical research, which may insert a bias in clinical findings and
409 therefore may lead to a disadvantage in clinical practice for women, is recognized and has been
410 described before[17,27,28,29]. Although we did not observe a significant gender bias in RD CTs,
411 we found that out of all studies recruiting only patients from a specific gender, twice as many
412 recruited only male patients than female, which could be partially attributed to the
413 aforementioned historic and general underrepresentation of women in CTs.
414 The age of eligibility for study subjects is crucial in many diseases, often influencing the overall
415 study success. The majority of RDs are thought to be genetic disorders, which present already
416 in early childhood or adolescence, thereby necessitating an early therapy start[30–32].
417 Consequently, RD CTs had a wide age range with the majority including pediatric patients,
418 unlike in more common diseases that can occur throughout life[17,26].
419 CT participation is often associated with great efforts by (pediatric) patients and their family
420 members, thus the study duration can have a major impact on participant compliance and
421 retention in the study. We found a direct correlation between the study duration and study
422 phase, which is in line with common clinical research practices such as monitoring procedures,
423 larger sample sizes, time to analyze larger data sets including side effects etc. in phase 3 studies.
424 The fact that industry-funded CTs are significantly shorter than academia-/non-profit-led CTs
425 could be attributed to the former usually having more resources, which allows for more sites,

426 thereby increasing patient recruitment velocity. Comparing RD CTs to all phases of nephrology
427 or cardiology studies, no significant difference could be detected in the overall study duration[14].
428 Clinical research is essential for clinical decision making and providing the best standard of
429 care for patients. Since the enactment of the FDAAA in 2007, CT result reporting is no longer
430 only ethically desirable, but also mandatory within twelve months upon trial completion.
431 However, this rule only applies to studies investigating a drug, biological or device
432 manufactured in the U.S. or studies indicating at least one study site in the U.S. or within its
433 territories[6]. Our analysis of studies completed before 2015 showed that after at least two years
434 following completion less than half of all analyzed RD CTs posted results on ClinicalTrial.gov.
435 A previous study on result reporting under FDAAA regulations found that only 22% of the
436 CTs report results timely, with only 10% doing so on a voluntary basis. Additionally, the
437 authors stated that result reporting occurs in only 40% of industry-funded and 9% not solely
438 industry-funded CTs with phase 3 studies being the most frequently reported CTs[7]. Despite
439 opposition of the FDA[33], an unofficial analysis conducted by the U.S. National Institutes of
440 Health (NIH) confirms that industry performs better than public sponsors (NIH and NIH-
441 funded), when it comes to timely result reporting, with 52% vs. 35%, respectively[34]. A recent
442 study analyzing the availability of phase 3 and 4 RD CT results on ClinicalTrial.gov found that
443 68% of the trials affected by the FDAAA reported results[35]. In our data set, phase 2 trials
444 account for roughly two thirds of the non-reporting CTs we identified. Studies registered with
445 the EU Clinical Trials Register (EUCTR), which requires result disclosure within 12 months
446 after trial completion, performed similarly, with only half of the applicable CTs posting
447 results[36]. This recent report also found that CT result reporting was linked to later study phases
448 and industry funding. Drawing a final conclusion on the result reporting rate between the two
449 sponsor categories in our data set is not obvious due to the incompleteness of the information
450 provided online. Considering only studies that clearly apply to the FDAAA, industry funding

451 is shown to be associated with a higher degree of non-reporting in RD CTs. However, including
452 potentially applicable CTs, academia/non-profit and industry fall abreast. This importantly
453 highlights the need for complete information in order for external parties to be able to draw
454 transparent conclusions. Generally, industry trials in RDs were associated with better overall
455 result posting even when not required by the FDAAA, potentially due to more strictly regulated
456 and overseen follow-up processes and the fact that industry-funded trials tend to be larger and
457 larger studies are more likely to be published[37].
458 The finding that RD CTs adhere more strictly to the FDAAA than CTs overall might be due to
459 ethical obligations towards these patients and the high value of clinical data from a CT, which
460 may be the only one performed in a patient population. RD CTs also include many pediatric
461 patients and pediatric CTs were found more likely to be completed[38]. Regardless of the reasons,
462 it is encouraging to note that RD CTs are reported at a higher rate than other CTs. Ultimately,
463 CTs need to overcome the widely recognized and general deficit of consistent and transparent
464 data sharing practices, not only to improve patient care, but also to value the participants who
465 help advancing science and future patients.
466
467 **CONCLUSION**
468 This study provides insights into the landscape of RD CTs. RD clinical research was found to
469 be rather industry-funded and focused on treatments involving drugs or biologicals, with many
470 studies including a relatively small number of participants and patients starting from very early
471 in life. Generally, industry funding was linked to larger trials, including higher enrollment and
472 more study locations, but slightly shorter study duration compared to academia/non-profit
473 trials. Finally, CTs in rare diseases make results more often publicly available than what has
474 been previously reported for all studies entered in ClinicalTrial.gov, but improvements are still
475 needed to make all data readily available for the public.

476

477 **Limitations**

478 There are some limitations in this study to be taken into consideration. First, ClinicalTrials.gov
479 does not cover all trials conducted worldwide. However, there is a reported 80% overlap
480 between ClinicalTrials.gov and the WHO ICTRP portal[18]. Secondly, there is no single standard
481 ontology for the description of clinical research and, despite extensive manual data curation
482 efforts, the data set may still contain misclassified studies. Conversely, some CTs may have
483 been excluded from our study, due to the disease under study not conforming to the ORDO
484 naming convention. Efforts were made to identify, correct or remove erroneous or ambiguous
485 as well as carelessly entered data prior to analysis, however, an element of uncertainty remains.
486 Additionally, a notable fraction of studies may provide divergent information on
487 ClinicalTrials.gov and EUCTR, making comparisons difficult[39]. Although the FDAAA was
488 introduced to increase transparency, this legislation came with certain limitations; For example,
489 its applicability to studies with at least one study site or an item manufactured in the U.S. or
490 U.S. territories. It is, however, not evident which studies are applicable and which ones are
491 exempt. Even though we attempted to address this limitation by examining a random sample
492 of 25% of the trials manually, errors may still be present. In this study, early proof-of-concept
493 trials, which can be impactful on the scientific community, e.g. in order to avoid duplicity of
494 resources, are not reviewed. Finally, this study represents a snapshot of RD CTs as they were
495 entered in March 2018 and some study details may have been added after we retrieved the data.

496

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597
598 **FIGURE LEGENDS**
599

600 **Figure 1.** *Flowchart showing the data set development including the applied filtering steps to*
601 *select the data sets for analysis. The first data set comprising 1,056 CTs conducted between*
602 *2008 and 2015 is used for the analysis of characteristics of RD CTs. The second data set*
603 *serves to investigate result publication practices among RD CTs.*
604
605 **Figure 2.** *Graphic representation of age restrictions for participants of the RD CTs in our*
606 *data set. Of the total of 1,056 CTs that were analyzed, 1,022 entered age specifications.*
607
608 **Figure 3.** *Comparison of study duration in months between industry- and academia/non-*
609 *profit-sponsored RD CTs. This analysis is based on the data set comprising 1,056 studies.*

610 **DECLARATIONS**

611

612 **Ethics approval and consent to participate**

613 Not applicable.

614

615 **Consent for publication**

616 Not applicable.

617

618 **Availability of data and materials**

619 The general datasets generated and analyzed during the current study are available in the
620 ClinicalTrials.gov repository, https://clinicaltrials.gov/. Moreover, the specific datasets used
621 and analyzed during the current study are available from Timothy J. Seabrook
622 (timothy_j.seabrook@roche.com) on reasonable request.

623

624 **Competing interests**

625 NKM was employed at F. Hoffmann-La Roche Ltd at the time of study conception, data
626 collection and analysis. JG, RRE, and TJS are employees of and hold shares in F. Hoffmann-
627 La Roche Ltd. We attest that we herein have disclosed any and all financial or other
628 relationships that could be construed as a conflict of interest and that all sources of financial
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630

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634

Authors' contributions

The study was conceived by JG, RRE, and TJS. Data acquisition, curation and analysis were performed by NKM. The results were interpreted by all authors. The manuscript was compiled by NKM and revised by JG, RRE, and TJS. All authors read and approved the final manuscript.

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Footnotes

Not applicable.