

PAPER

Terminating clinical trials without sufficient subjects

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ABSTRACT

Medical research involving human subjects can be risky and burdensome. Therefore, such research must be reviewed and approved by a Research Ethics Committee (REC). To guarantee the safety of the subjects, it is very important that these studies be conducted in accordance with the approved protocol. An important issue in this respect is whether studies include the requisite number of subjects based on the research question. The research question is unlikely to be answered reliably if the requisite number of subjects is not met. In such cases, subjects are exposed to unnecessary risks and burdens. In this descriptive study, the authors evaluated how frequently studies are completed with the required number of subjects. Moreover, the authors identified the characteristics of research that does and does not include the required number of subjects. The results of this study show that a considerable proportion of studies (41/107) were terminated although they failed to recruit a sufficient number of subjects. Furthermore, the authors found that investigator-initiated studies have significantly ($p=0.028$) more problems in recruiting the requisite number of subjects than studies initiated by pharmaceutical companies. Potential solutions are discussed to reduce the number of studies that do not include a sufficient number of subjects.

INTRODUCTION

Medical research involving human subjects is ethical only if it fulfils a number of scientific and ethical requirements.^{1–3} The main scientific requirements are relevance, originality and the methodological correctness of the research. The ethical requirements include a fair risk-benefit ratio and the autonomy of the participants.

Another important ethical requirement is the minimisation of risks and burdens. This requirement means that no study procedure is performed if it is not strictly needed to answer the research question. Furthermore, the minimisation requirement implies that only the number of subjects necessary to answer the research question is included.

In The Netherlands, as in most countries, a Research Ethics Committee (REC) must review medical research involving human subjects.⁴ RECs assess whether the research proposal meets the corresponding scientific and ethical requirements. One of the key issues is whether it is possible to answer the research question using fewer subjects than proposed in the protocol. A review is used to determine whether the number of subjects in the approved research protocol is sufficient and absolutely necessary to answer the (primary) research question.

The question is whether research studies approved by RECs are actually completed with the number of subjects listed in the approved protocol. We have reason to doubt this because finding eligible subjects is a notorious problem, also known as Lasagna's Law.^{5–8} Moreover, difficulties recruiting a sufficient number of subjects are often reported to our REC.

To answer the abovementioned question, we examined all trials submitted in 2004 to our regional REC, one of the three largest committees in the Netherlands (with respect to the average number of submitted studies over the course of a year). We examined the 2004 files because most of the trials do not run for more than 5 years. Therefore, most of the studies submitted for approval in 2004 were expected to be completed in 2010. Our main point of interest was the number of subjects who were actually included and the difference between this number and the number that was needed according to the approved protocol. We attempted to identify the similarities and differences between trials that did and did not include the required number of subjects.

The results of our study are interesting. A considerable percentage of studies were terminated before the inclusion of the indicated number of subjects. This phenomenon was frequently observed in investigator-initiated studies. This finding indicates a serious situation from both a scientific and an ethical point of view. In the studies that did not include the requisite number of subjects, the soundness of the findings should be doubted. Furthermore, participants in these studies were unnecessarily exposed to burdens and risks.

We will address the question of what can be done to solve this problem. In particular, we will consider which stakeholders could contribute to ensuring that the required number of subjects is included in the study.

STUDY METHODS

In our study conducted in 2010, we examined all study files that were submitted to our REC in 2004 and were subsequently approved.

Approval was granted to 166 trials. We assessed whether each study was reported as completed. If there was no report of study termination, we asked the investigator by email whether the study was ongoing. For the completed studies, we determined the number of subjects that were actually included and the number of subjects that should have been included. If not already available, we asked the investigator for a publication describing the study. Furthermore, we created an inventory of seven study characteristics that, in our opinion, were

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likely to influence whether the study was completed correctly: the type of research (eg, initiated by a pharmaceutical company or investigator, single-centre or multi-centre study) the type of subjects (patients or healthy volunteers, vulnerable or not vulnerable, including those not able to provide informed consent) and the risks, burdens and advantages incurred by the subjects (risks, withholding of regular therapy and provision of a reward). In table 3, these characteristics are classified according to the supposed degree of influence of these respective characteristics on the main outcome of our study, trials including an insufficient number of subjects.

STUDY FINDINGS

Almost 75% of 166 approved studies were reported as completed (n=123) (table 1). Of the remaining 43 studies, data were lacking in 12 studies, six studies failed to begin and 25 studies were ongoing. Eight of these 25 studies (32%) remained within their estimated duration. The estimation of the study duration is an inextricable part of the proposal. It is expected that investigators base their estimations on realistic figures, which is the number of eligible subjects normally seen on a yearly basis in the participating study centres. A considerable portion of the 25 studies (n=11 ie, 44%) was delayed because of problems in recruiting subjects. Considering the degree of the delay, the likelihood that these studies will be completed successfully must be reconsidered. The remaining six studies were delayed due to practical problems (eg, an investigator on maternal leave, difficulties with drug supplies), or the exact reason for the delay was unknown.

Among 123 completed studies, 107 studies were included in the final analysis. Sixteen studies were excluded for several reasons (table 2). Seven studies were excluded because they lacked the required number of subjects for legitimate reasons, such as safety problems or a lack of efficacy, often according to termination rules predefined in the protocol. One study was prematurely ended for unknown reasons. For eight studies, information pertaining to the number of subjects could not be obtained.

Approximately 60% (n=66) of the remaining 107 studies included the number of subjects that should have been included according to the protocol. Remarkably, 13 studies (12%) included more subjects than reported in the REC-approved protocol. In nine of these studies (70%), over 10% more subjects were included (range 18–166). However, fewer subjects than required were included in 41 out of 107 studies. In four studies, this deficit was limited to <10%, but in majority (n=37) of these studies, the deficit of participants exceeded 10% (ie, 10–95 fewer subjects than described in the protocol).

Characteristics of the 107 completed studies included in the analysis

Over 75% of the studies were investigator initiated. The remaining 25% were initiated by a pharmaceutical company

Table 1 Status of all studies at the time of analysis

	n (%)
Completed studies	123 (74)
Studies that were never started	6 (4)
Ongoing studies	25 (15)
Unknown	12 (7)
Approved studies	166 (100)

(table 3). There are far more single-centre studies than multi-centre studies (63.5% and 36.5%, respectively). In general, the study subjects were patients (87%), but 13% of the studies were performed on healthy subjects only. Few studies were performed with vulnerable subjects, defined as minors or subjects unable to provide informed consent (7%). Usually, studies involved certain risks (79%). In a minority of the studies (13%), subjects ran the risk that a regular therapy for their illness would be withheld. In majority of the studies (79%), subjects did not receive a reward for their participation.

Almost half (46%) of the investigator-initiated studies were terminated before the requisite number of subjects was reached. This percentage was notably lower in studies that were initiated by a pharmaceutical company (12.5%). This trend is in line with the fact that most investigator-initiated studies are single-centre studies, whereas multi-centre studies are typically initiated by pharmaceutical companies.

In contrast to expectations, in-patient trials had only slightly more difficulty obtaining the indicated number of subjects than studies of healthy subjects (60% and 71%, respectively).

Another notable finding was that studies with no risks for the participants had more difficulty reaching the projected number of subjects than studies that did pose risks to the participants (43.5% and 67%, respectively).

Only seven studies were performed with vulnerable subjects, and more than half of these (n=4) failed to include the indicated number of subjects.

Studies rewarding subjects for participation were not substantially successful in reaching the projected number of subjects than studies with no reward other than reimbursement for travelling expenses (70% and 60%, respectively).

We used logistic regression to determine which trial characteristics were indicators that a sufficient number of subjects had been included (table 3). Four variables were selected in advance and included in this analysis: (1) initiation by an investigator or by a pharmaceutical company, (2) the inclusion of patients or healthy subjects, (3) studies with or without risks to participants, (4) studies with or without the risk that regular therapy would be withheld. The analysis revealed that the first factor, the initiator of the studies, is an important indicator for achieving the number of subjects needed (p=0.028).

Table 2 The features of completed studies

	n (%)	Required number of subjects	
		Reached, n (%)	Not reached, n (%)
Studies prematurely terminated due to the protocol criteria (safety, lack of efficacy)	7 (6)		
Studies prematurely terminated for unknown reasons	1 (1)		
Number of subjects included was unknown	8 (7)		
Studies included in the analysis: completed and number of subjects included was known	107 (86)	66 (62)	41 (38)
Studies completed	123		

Table 3 Characteristics of 107 studies with the number of included subjects known

Characteristic	Required number of subjects reached (n=66) n (%)	Required number of subjects not reached (too low) (n=41) n (%)	Univariate analysis χ^2 -square test (p-value)	Multivariate analysis: logistic regression (p-value)
Initiated by pharmaceutical company (n=24, 22%)	21 (87.5)	3 (12.5)	0.003	0.028
Initiated by investigator (n=83, 78%)	45 (54)	38 (46)		
Subjects: patients (n=93, 87%)	56 (60)	37 (40)	0.421	0.207
Healthy subjects (n=14, 13%)	10 (71)	4 (29)		
Without risks (n=23, 21%)	10 (43.5)	13 (56.5)	0.043	0.410
Not without risks (n=84, 79%)	56 (67)	28 (33)		
Chance regular therapy withheld (n=14, 13%)	12 (86)	2 (14)	0.047	0.398
Regular therapy not withheld (n=93, 87%)	54 (58)	39 (42)		
Reward (n=23, 21%)	16 (70)	7 (30)	0.380	
No reward (n=84, 79%)	50 (59.5)	34 (40.5)		
Single-centre (n=68, 63.5%)	37 (54)	31 (46)	0.041	
Multi-centre (n=39, 36.5%)	29 (74)	10 (26)		
Vulnerable subjects (n=7, 7%)	3 (43)	4 (57)		
No vulnerable subjects (n=100, 93%)	63 (63)	37 (37)		

In addition, we again used logistic regression to conduct an explorative analysis of the relationship between the inclusion of the requisite number of subjects and the following factors: (1) initiation by an investigator or pharmaceutical company, (2) use of a reward or no reward, and (3) a single-centre or multi-centre design. This analysis confirmed that the initiator of the study was the only important factor ($p=0.022$) (reward or no reward ($p=0.210$) and single-centre or multi-centre ($p=0.856$)). Thus, the univariate association with single/multi-centre design ($p=0.041$, table 3) was no longer valid.

DISCUSSION

Our study revealed three notable findings.

First, a considerable number of the approved studies that were included in the analysis (41/107 ie, 38%) were terminated before the required number of subjects was obtained and without reference to predefined termination rules. Twenty-five (15%) studies approved in 2004 (n=166) were severely delayed. It is doubtful whether these studies will be completed properly.

Second, the initiator (sponsor) of the study is the most important factor in achieving the required number of subjects, with investigator-initiated studies failing more often than pharmaceutical company-initiated studies.

Third and remarkable, approximately 10% of the studies included more subjects than needed according to the protocol (over 10% more participants in 70% of these cases). This deviation from the protocol occurred more often in investigator-initiated studies.

Regarding the last point, we did not ask the researchers why more subjects were included than were needed to answer the primary research question. This question fell outside the scope of our study. In large multi-centre studies, a minor excess in the number of participants with respect to the fixed number may be unavoidable for logistical reasons. However, if in some cases, the number of subjects were increased to obtain statistically significant results, this would represent a very serious methodological flaw.

The first two findings draw attention to a serious problem. Including fewer subjects than the requisite number is problematic from both scientific and ethical points of view. The value and validity of the principal study results would be questionable, and study subjects would have participated in these studies needlessly.

The problem of including fewer subjects is much more common in investigator-initiated studies than in pharmaceutical company-initiated studies. This finding might be explained by

the fact that pharmaceutical companies have a larger budget and a better infrastructure for research that allows them to carefully monitor the progress of the study and to adapt the protocol (eg, increase the number of sites, adapt the recruitment strategy), if necessary. Moreover, studies by pharmaceutical industries usually do not rely on a single investigator, so continuation is more likely. In recent years, hospitals have tended to facilitate clinical trials by creating a specialised research department. An increasing number of independent research networks for specific diseases, such as the European Organisation for Research and Treatment of Cancer (EORTC), have been started, which may improve the quality of investigator-initiated trials. The question is what can and should be done to solve or to reduce this problem.

Investigators should pay careful attention to the feasibility of their studies. They should make realistic estimations of the number of subjects available in theory and the numbers that are expected to provide consent and to drop out. These estimations should be specified in study protocols.⁹ The review of these estimations should be an inextricable part of the review by RECs.

Furthermore, researchers should meticulously monitor the inclusion rate during the course of the study. The results of our study raise the question of whether RECs should also monitor the inclusion rate. The role of RECs in monitoring ongoing studies is not clear. In practice, their role is limited to reviewing amendments and serious adverse events. According to the Declaration of Helsinki, monitoring ongoing research is not mandatory, but RECs are allowed to do so. Is it reasonable and advisable for RECs to use this right and monitor the inclusion rate? Answering this question is beyond the scope of this article. However, we can provide a few suggestions. The answer may depend on which of the two perspectives on the role of RECs is adopted. In one paradigm, RECs' main task is to ensure that nothing happens to a research subject without his valid consent. In the other, RECs' primary role is to protect subjects from harm.^{10 11} Supporters of the first view may see a role for RECs in monitoring the informed consent procedure, but surely not in monitoring the inclusion rate. By contrast, for supporters of the role of RECs as protectors of research participants against harm, the need for monitoring the accrual is more obvious.

A first step in this monitoring could be creating an obligation for researchers to report regularly on the inclusion rates of their studies, particularly in studies for which not many subjects are expected to participate.

To prompt investigators to terminate their research with the specified number of subjects, it should be mandatory for investigators to register their protocols in a public trial register.^{12–17} Important developments have been introduced by scientific journals, such as requiring investigators to sign their agreement to the Consort statement. These modifications guarantee that editors have access to the full protocol and can verify whether a study described in a submitted paper was conducted and analysed according to the protocol approved by an REC.^{18–22} In our study, we found that few study results are published: 40% of the studies that included the correct number of subjects were published compared with 32% of the studies that did not obtain the requisite number of subjects. It is noteworthy that in the latter publications, these protocol violations were reported only twice.

Finally, because financial means are likely to play a role in investigators' ability to achieve a successful inclusion rate, we suggest that the policies of the government and other authorities consider this aspect.

CONCLUSION

Our study results indicate the difficulty in including the number of subjects necessary to answer (primary) research questions. This problem typically occurs in investigator-initiated studies. These findings are disturbing from both a scientific and an ethical point of view. Therefore, the problem must be addressed. The investigator who is the first responsible party should thoroughly estimate the feasibility of attaining the required number of subjects and monitor the inclusion rate. However, other stakeholders can contribute to resolving or reducing this problem. Scientific journals can thoroughly verify whether submitted articles are in complete agreement with the study protocol as approved by RECs. RECs in turn should be much more critical of the feasibility of studies before granting institutional approval. It is debatable whether RECs should also play a role in monitoring the inclusion rates of ongoing studies.

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