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Data & Safety Monitoring Boards in Industry-Sponsored Clinical Trials

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Abstract

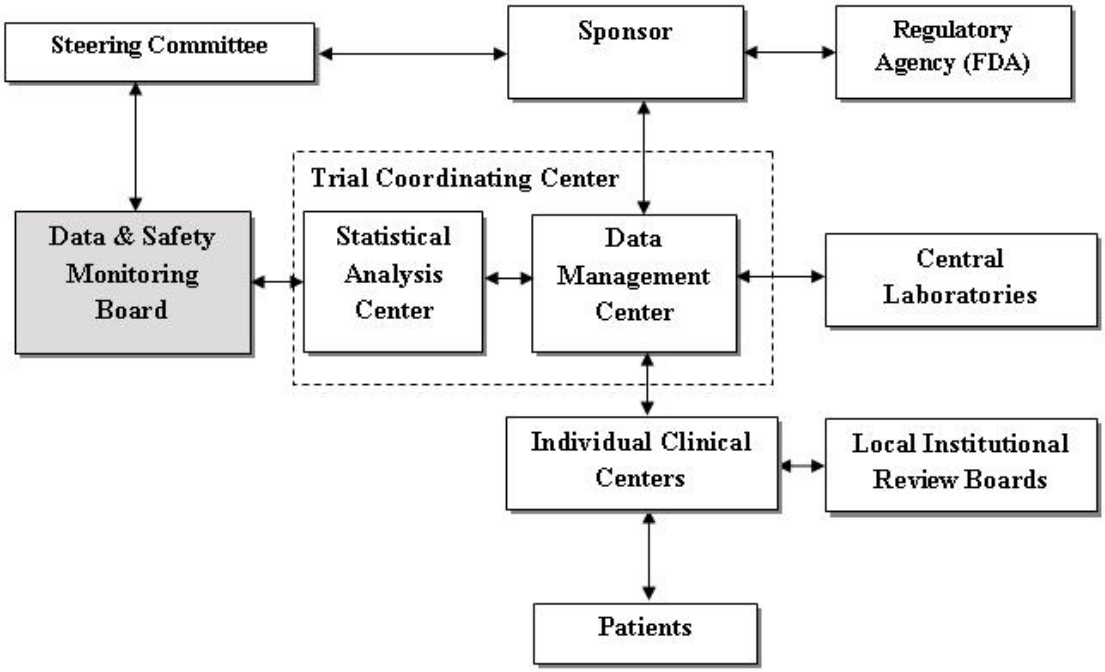
The frequency of reported use of a Data & Safety Monitoring Board (DSMB) in industry-sponsored clinical trials and characteristics of trials involving a DSMB were investigated. Protocols and clinical trial agreements (CTAs) for 32 industry-sponsored trials (21 drug and 11 device) were reviewed. Based on the protocol review, 19 trials (59%) used a DSMB, while none of the reviewed clinical trials agreements (CTAs) mentioned a DSMB. The best predictors of DSMB use were: (a) survival as a primary endpoint, (b) surgery or a drug administered once as treatment, (c) the investigation of a Class III-risk medical device, and (d) conduct of the trial only in U.S. vs. internationally. Relatively frequent use of a DSMB (although statistically nonsignificant) was noticed for: (a) Phase II and III compared to phase IV trials, (b) trials with a relatively large number of subjects, (c) trials with a long follow-up period, and (d) open-label compared to double-blind trials.

Background

A randomized controlled trial (RCT) provides the highest level of methodological rigor for evaluating the efficacy and safety required for regulatory approval and market entry of investigational drugs, medical devices, and biologics. The U.S. Food and Drug Administration (FDA) mandates that "clinical trials of new drugs are designed and carried out in a manner that will insure the integrity and validity of the study inferences." [1] An important component of this process is data and safety monitoring, defined as the activity of reviewing the data collected, with the goal of protecting the safety of the participants, the credibility of the trial, and the validity of the results. NIH requires data and safety monitoring for "all types of clinical trials, including physiologic, toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); and efficacy, effectiveness and comparative trials (Phase III)." [2] Similarly, the FDA,[3] the European Agency for the Evaluation of Medicinal Products,[4] and the World Health Organization[5] have issued guidelines on this topic.

It is thus now common in both federal- and industry-sponsored clinical trials to establish a DSMB of independent experts who have access to unblinded interim data. First introduced in the 1960s, DSMBs represent an important mechanism for protecting subjects in clinical trials. The committee is known by different names. The most commonly used names are Data & Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), and Treatment Effects Committee (TEC). Since the term Data & Safety Monitoring Board (DSMB) was used in all the trials reviewed in this study, for consistency we preferred this terminology. Figure 1 describes the organizational structure of a commonly used model for industry-sponsored clinical trials with emphasis on the relationships among the DSMB and other groups involved.

Figure 1. A Commonly Used Model for Industry-Sponsored Clinical Trials*



* Adapted from De Mets et.al.[6]

The Extent of DSMB Use in Industry-Sponsored Clinical Trials

In 2002, the New England Journal of Medicine published an article that raised significant concerns about whether industry-sponsored trials are using DSMBs. In this article, Shulman et al.,[7] after reviewing the clinical trial agreements (CTAs) between industry sponsors and 108 academic institutions, found that only 1% of these CTAs mentioned the use of a DSMB.

Kiri et al.[8] and Sydes et al.[9] explored the use of DSMBs in industry-sponsored clinical trials using published trial reports rather than CTAs. Kiri and colleagues reviewed 562 clinical trials with sample sizes >200 published between 1990 and 1995 in seven major journals. The authors found that 42% of 206 industry-sponsored trials had a DSMB. Similarly, Sydes and colleagues found that 24% of 304 industry-sponsored clinical trials published in 2000 in six general and 16 specialty journals had a DSMB.

The large discrepancies in these three studies encouraged us to investigate the frequency of DSMB use in a sample of industry-sponsored clinical trials conducted at our institution using as the source of information both the protocols and the clinical trial agreements (CTAs). Our first hypothesis was:

H1: Protocols would mention DSMB use more frequently than CTAs.

Which Trials Need a DSMB?

In a comprehensive review of published studies related to the practices and operations of DSMBs, the DAMOCLES group (Data Monitoring Committees; Lessons, Ethics and Statistics)[10] summarized characteristics of trials that may need a DSMB. Table 1 describes these characteristics:

Table 1. Characteristics of Trials that May or May Not Need a DSMB*

TRIALS THAT MAY NEED A DSMB	TRIALS THAT MAY NOT NEED A DSMB
High profile, pivotal trials likely to have profound effect on clinical practice	Trials aimed to demonstrate a biological principle
Trials with vital status as an outcome measure	Trials in which there are minor hazards from treatment
Trials in which the risks are unknown	Trials with short duration
Trials with long duration	Behavioral and administrative trials
Blinded trials	
Trials in vulnerable populations (e.g., elders, pregnant women, children)	

* Adapted from Grant et al.[10]

In developing criteria for reviewing our sample of industry-sponsored clinical trials, we considered several findings of the DAMOCLES group.

Special considerations are involved when the trial investigates a device. Medical devices are regulated in the U.S. by the FDA Center for Devices and Radiological Health (CDRH). The process of obtaining FDA approval is determined by the perceived risk associated with the device. Devices are classified in three categories: Class I, II and III. Class I devices (lowest risk, for example, elastic bandages), include 47% of the medical devices according to FDA and do not require FDA review before market introduction. Class II devices (moderate risk, for example, powered wheelchairs and haemostatic bandages) include 43% of medical devices according to FDA, and require FDA clearance of a premarket notification (PMN) application (i.e., 510[k]) and proof that the new device is "substantially equivalent" to a legally marketed device before the device is marketed. Class III devices (highest risk, for example, coronary stents and heart valves) include 10% of medical devices according to FDA, and require FDA clearance of a premarket approval (PMA) application and a reasonable assurance that the device is safe and effective in the target population before it can be marketed.

Our second hypothesis was:

> H2: Trials are more likely to use a DSMB if they are relatively risky for the subjects or if adverse events will more likely cause problems for the sponsor, site and IRB.

Therefore, we examined risk-related trial characteristics that may be associated with the use of DSMB in a sample of industry-sponsored trials.

Methods

Thirty-two industry-sponsored clinical trials currently enrolling patients at Charleston Area Medical Center in Charleston, West Virginia, were included in the study. The data collection sheet included the presence or absence of a DSMB and 10 risk-related predictors associated with our second hypothesis. For each predictor, we formulated a hypothesis (labeled H2.1-H2.10):

1. Type of treatment (drug vs. Class II or III device) – H2.1: Class III device trials are riskier than Class II device and drug trials.

2. Phase (II,III,IV) – H2.2: Phase II and III pre-approval trials are riskier than Phase IV post-approval trials.
3. Therapeutic area (cardiovascular, neurology, other) – H2.3: Trials in the cardiovascular and neurology areas are riskier than trials in other areas.
4. Presence of a survival endpoint (yes, no) – H2.4: Trials with a survival endpoint are riskier than trials without one.
5. Countries in which the trial was conducted (U.S.-only vs. multinational) –H2.5: Sponsors prefer to conduct riskier trials in the U.S. only.
6. Planned sample size (<100, 100-499, 500-999, 1000+) – H2.6: Larger trials are more challenging to conduct and any problems that appear will have more serious ramifications for sponsors than smaller trials.
7. Type of subjects (adults vs. children) – H2.7: Sponsors, sites and IRBs are more sensitive to risks for pediatric than adult subjects.
8. Study design (double-blind, single-blind, open-label) – H2.8: Sponsors are more likely to choose an open-label design for riskier studies. (The sponsor might use an open-label design for treatments that can't be blinded, i.e., surgery and also for treatments with a long follow-up duration.)
9. Treatment duration (surgery/drug administered only once, drug administered for less than 3 months, drug administered between 3 months and 2 years, and drug administered for more than 2 years) – H2.9: (a) Surgery trials are riskier than non-surgery trials; and (b) Trials in which drugs are administered only once most commonly involve acute severe conditions; e.g., strokes and heart attacks, and therefore are riskier.
10. Follow-up duration (≤3 months, 3 months-2 years, ≥2years) –H2.10: Longer follow-up periods indicate the possibility of longer-term risks or more importance of the study to the sponsor.

Two independent raters reviewed the protocols and CTAs. The average coefficient of concordance (Cohen's kappa) between the two raters for the 10 predictors and DSMB use was 98%. When differences occurred, a referee resolved them.

Data were entered into a database and analyzed using SPSS 14.0. Descriptive statistics were computed for each variable using percentages.

In the first step, the significance of differences in DSMB use in trials characterized by each of the 10 predictors was determined. Due to the small sample size (less than 5 cases for some cells in the comparisons), statistical significance was investigated using the binomial rather than the chi square test. Additionally, for dichotomous predictors, the statistical significance was investigated using Fisher's exact test.

In the second step, predictors for which a statistically significant difference in DSMB use was noticed were further evaluated using logistic regression. Due to the small sample size, we limited our analysis to a determination of the percent of variance in DSMB use (Nagelkerke R square) based on the significant predictors, using univariate rather than multivariate logistic regression. Additionally, the relationships between the predictors were determined using the Spearman correlation coefficient. All statistical tests were considered significant if $p<.05$.

Results

Extent of DSMB use

Nineteen (59%) of 32 protocols mentioned a DSMB. However, none of the CTAs mentioned a DSMB.

Predictors

Table 2 describes the prevalence of DSMB use based on the ten predictors listed above.

1. Type of Treatment

Overall, the presence or absence of a DSMB in drug versus device trials was statistically nonsignificant (p=.12, two-tailed Fisher's exact test). Post-hoc comparison between device trials with and without a DSMB approached significance (p=.06), with most of the device studies (82%, 9 out of 11) having a DSMB. A further classification of the devices according to risk indicated that all nine device trials with a DSMB investigated a Class III-risk device while the two device studies without a DSMB were for a Class II-risk device (p=.01, two-tailed Fisher's exact test).

2. Phase

Twenty three (72%) of the reviewed trials were Phase III. It was observed that more Phase II (75%) and Phase III (61%) compared to Phase IV (40%) trials had a DSMB. However, these differences were not statistically significant (see Table 2). Further analysis revealed a similar distribution of drug versus device trials across phases. For Phase II, 50% (n=2) of the trials were drug and 50% (n=2) were device trials; for Phase III, 70% (n=16) were drug and 30% (n=7) were device trials; and for Phase IV, 60% (n=3) were drug and 40% (n=2) were device trials.

3. Therapeutic Area

Most of the trials were in the cardiovascular area (56%, n=18) or neurology (25%, n=8). Nineteen percent of the trials (n=6) were in other therapeutic areas. No significant differences in the use of a DSMB were observed among these clinical domains. All 11 device trials were in the cardiovascular area, while the 21 drug studies were distributed equally among the three domains: 33% (n=7) in the cardiovascular, 38% (n=8) in neurology, and 29% (n=6) in other areas. When considering drug trials only, the percentages of DSMB use across the therapeutic areas were similar: 43% (n=3) for cardiovascular, 50% (n=4) for neurology and 50% (n=3) for other therapeutic areas.

4. Survival Endpoint

Forty percent of the trials (n=13) specified mortality as an endpoint. All of these studies had a DSMB (p<.001, two-tailed Fisher's exact test). A further comparison of drug versus device studies based on the presence or absence of a survival endpoint indicated that only 29% (n=6 out of 21) of the drug versus 64% (n=7 out of 11) of the device studies had mortality as an endpoint (p=.07, two-tailed Fisher's exact test). Out of 9 Class III-risk devices with a DSMB, 78% (n=7) had survival as an endpoint. Out of 10 drug trials with a DSMB, 60% (n=6) had survival as an endpoint.

	DSMB (n=19)	Total (N=32)	%	95% CI	p value for the binomial test (50% cutoff)
Treatment					
Drug	10	21	48%	(26%-70%)	1.00
Class II device	0	2	0%	(0%-84%)	0.50
Class III device	9	9	100%	(66%-100%)	.004*
Trial Phase					
II	3	4	75%	(19%-99%)	0.62
III	14	23	61%	(39%-80%)	0.40
IV	2	5	40%	(5%-85%)	1.00
Therapeutic Area					
Cardiovascular	12	18	67%	(41%-87%)	0.23
Neurology	4	8	50%	(16%-84%)	1.00
Other	3	6	50%	(12%-88%)	1.00
Survival Endpoint					
Yes	13	13	100%	(75%-100%)	<0.001**
No	6	19	32%	(13%-57%)	0.16
Country					
US only	13	17	77%	(50%-93%)	0.05*
US + Others	6	15	40%	(16%-68%)	0.60
Planned Sample Size					
<100 patients	1	3	33%	(0.8%-91%)	1.00
100-499 patients	8	16	50%	(25%-75%)	1.00
500-999 patients	4	6	67%	(22%-96%)	0.68
1000+ patients	6	7	86%	(42%-100%)	0.12
Population					
Adults	18	27	67%	(46%-84%)	0.12
Children	1	5	20%	(1%-72%)	0.37
Design					
Double blind	9	18	50%	(26%-74%)	1.00
Single blind	1	2	50%	(1%-99%)	1.00
Open-label	9	12	75%	(43%-95%)	0.14
Treatment Duration					
Administered once	12	15	80%	(52%-96%)	0.03*
≤ 3mo	2	9	22%	(3%-60%)	0.18
3 mo-2y	2	4	50%	(7%-93%)	1.00
≥2y	3	4	75%	(19%-99%)	0.625
Follow-up Duration					
≤ 3mo	5	9	56%	(21%-86%)	1.00
3 mo-2y	7	14	50%	(23%-77%)	1.00
≥2y	7	9	78%	(40%-97%)	0.18

Table 2. Percentage of Trials with a DSMB According to 10 Predictors

* significant at p≤.05, ** significant at p<.001

5. Countries

All trials were multicenter, with 47% multinational (U.S. and other countries). Comparison between U.S.-only and multinational trials for use of DSMBs indicated that U.S.-only trials used a DSMB significantly more frequently (77%) than multinational trials (40%) (p=.05). However, because all of the device studies were conducted only in the U.S. and 82% of the device studies used a DSMB, we considered the possibility that the significant tendency observed initially was due to a confound (the difference in the treatment type rather than the country). A separate analysis revealed that, in contrast to the device studies, most of the drug studies (71%) were multinational. A comparison of DSMB use in U.S.-only versus multinational drug trials indicated that 67% of U.S.-only trials had a DSMB compared to 40% of multinational trials. However, this difference was not statistically significant (p=.36, two-tailed Fisher's exact test).

6. Planned Sample Size

Half of the studies (n=16) had a planned sample size between 100 and 499 subjects. A statistically nonsignificant trend towards use of DSMBs for larger trials was observed (33% of trials with <100 subjects, 50% of trials with 100-499 subjects, 67% of trials with 500-999 subjects, and 86% of trials with 1000+ subjects). A further analysis based on the drug vs. device distinction indicated similar percentages for each planned sample size across the two study types (see Table 3).

Table 3. Sample Size Distribution Across Drug and Device Trials

	<100 patients (%)	100-499 patients (%)	500-999 patients (%)	1000+ patients (%)	Total
Drug	2 (9%)	10 (48%)	5 (24%)	4 (19%)	21
Device	1 (9%)	6 (55%)	1 (9%)	3 (27%)	11

7. Population

Most of the reviewed trials (84%) were conducted with adults. Although DSMBs were used more in adult (67%) than in pediatric trials (20%), this difference was not statistically significant (p=.13, two-tailed Fisher's exact test). However, all of the device trials were conducted in adults. Out of 16 drug studies conducted in adults, 56% (n=9) had a DSMB. Twenty percent (n=1) of the 5 drug pediatric trials used a DSMB.

8. Design

A majority of the studies used double-blind (56%, n=18) or open-label (37%, n=12) designs, with only 6% (n=2) using a single-blind design. No significant statistical differences in the use of a DSMB for different study designs were found. We compared the type of design in drug vs. device trials including only the double-blind and open-label trials (see Table 4). Most drug trials used a double-blind design (76% double-blind vs. 24% open-label), while most device trials used an open-label design (78% open-label versus 22% double-blind), (p=.01, two-tailed Fisher's exact test). This difference can be explained by the difficulty of conducting double-blind device trials. Out of 16 double-blind drug studies, 44% (n=7) used a DSMB. Out of 5 open-label drug studies, 60% (n=3) used a DSMB. Six out of seven (86%) open-label device trials used a DSMB.

Table 4. Design Characteristics Across Drug and Device Trials

	Double-blind (%)	Open-label (%)	Total
Drug	16 (76%)	5 (24%)	21
Device	2 (22%)	7 (78%)	9

9. Treatment Duration

Eleven studies investigated surgery and four studied a one-time drug administration. A statistically significant tendency to use a DSMB was noticed for trials investigating surgery or one-time drug administration (p=.03). The 11 studies investigating surgery were all for devices and 82% (n=9) used a DSMB. Out of 4 studies with a one-time drug administration, 75% (n=3) used a DSMB and all were for an acute condition (stroke or heart attack). A similar percentage 75% (n=3) of DSMB use was noticed for drugs administered for 2 years or longer. In contrast, only 22% (n=2) of drug trials with a treatment duration of less than 3 months used a DSMB.

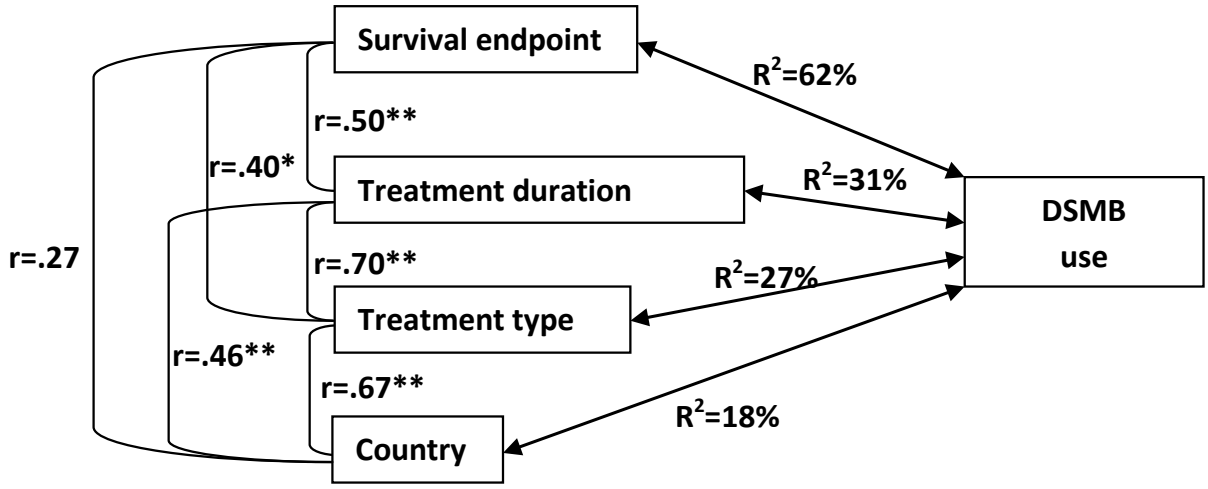
10. Follow-up Duration

A statistically nonsignificant tendency for a higher frequency of DSMB use in trials with long follow-up periods was noticed (56% DSMB use in trials with a follow-up period shorter than 3 months, 50% use in trials with a follow-up period between 3 months and 1 year, and 78% DSMB use in trials with follow-up periods longer than 2 years).When only the drug studies were considered, 80% of the trials with a follow-up duration longer than 2 years used a DSMB. Only 25% of the drug studies with a follow-up between 3 months and 1 year used a DSMB. When the follow-up was studied only for acute conditions (the three studies with a one-time drug administration that used a DSMB), all these studies had a short follow-up duration (less than 3 months).

Univariate Logistic Regression Analysis

The predictors identified as significant using binomial and Fisher's exact tests were explored further using univariate logistic regression. The predictors included were: survival endpoint (yes, no), treatment duration (surgery/drug administered once, drug administered for less than 3 months, drug administered between 3 months and 2 years, drug administered for more than 2 years), treatment type (drug, Class II device, Class III device), and country (U.S.-only, multinational). The criterion evaluated was presence vs. absence of a DSMB. The percentage of variance explained by each predictor was reported using Nagelkerke R square. Figure 2 shows the percentage of variance explained by each predictor as well as the Spearman correlation coefficients between the predictors.

Figure 2. Percentage of Variance Explained by Each Predictor and Intercorrelations Between Predictors



* Significant at p<.05 ** Significant at p<.001

Discussion

Extent of DSMB use

Consistent with our first hypothesis, the use of a DSMB was mentioned more frequently in trial protocols than in CTAs. Nineteen (59%) of the clinical trials reviewed used a DSMB. In all of these cases, DSMB use was mentioned only in the protocols and not in the CTA. Therefore, it is not surprising that Shulman et al. identified DSMB use in only 1% of industry-sponsored trials by reviewing CTAs (since CTAs typically include protocols as attachments). The difference in our finding (59%) versus those of Kiri et al. (42%) and Sydes et al. (24%) are probably due to differences in the study population sampled. When we considered only the cardiovascular and neurology areas, our results and those of Kiri et al. were very similar. Thus, for trials in the cardiovascular area, we identified a DSMB in 67% of the trials, and Kiri et al. found a DSMB in 65% of the trials. For trials in the neurology area, we found a DSMB in 50% of the trials and Kiri et al. found them in 47% of the trials.

Characteristics of Trials that Use DSMBs

Consistent with our second hypothesis, eight of 10 differences in the use of DSMB were in the predicted direction. The two exceptions were (a) a reversed difference in DSMB use in adult vs. pediatric trials (higher in adults versus pediatric), and (b) no difference in DSMB use among cardiovascular, neurology and other therapeutic areas. Four of the eight confirmed differences were statistically significant and four nonsignificant. Significantly higher DSMB use was found for (a) trials with survival as a primary endpoint, (b) trials investigating a Class III-risk device, (c) trials investigating surgery or one-time drug administration, and (d) trials conducted in the U.S.-only. Statistically nonsignificant trends for higher DSMB use were found for: (a) Phase II and III compared to Phase IV trials, (b) trials with a larger sample size, (c) open-label versus double-blind trials, and (d) trials with a long treatment follow-up period.

Of special interest is the very high percentage (100%) of DSMB use in trials with a survival endpoint. Although perhaps not surprising, the percentage was higher than the findings

reported in Kiri's et al. (64%) and Sydes's et al., (33%) studies. The findings may reflect an overall higher level of risk for the trials involved in our study compared to the two other studies.

Similarly, the percentage of DSMB use for device trials in our study was significantly higher (82%) than that reported in Kiri's et al. (47%). Since Kiri et al. did not report the type of device investigated (Class II vs. Class III), the observed difference may be explained by a higher percentage of Class III (highest-risk) devices in our study.

Relatively frequent use of a DSMB in trials investigating a one-time drug administration may be determined by the acute nature of the condition treated (stroke or heart attack) rather than the one-time nature of the treatment itself. Therefore, for our sample, we consider drug-administered-once an indirect index of a more acute condition.

The trend towards more frequent use of DSMBs in Phase II and III vs. Phase IV trials can be explained by the main characteristics of Phase IV trials: postmarketing, with risks already investigated in the previous phases.

More frequent use of DSMBs in trials with a relatively large planned sample size (67% DSMB use for samples between 500 and 999, and 86% DSMB use for samples larger than 1000) is consistent with Kiri's et al., data (58% DSMB use for trials with a sample size larger than 524 patients) and Sydes's et al., findings (71% DSMB use for samples larger than 1000).

Considering that children are a vulnerable population, we predicted that DSMB use would be more prevalent in pediatric than adult trials. However, due to the small number of pediatric trials in the study (n=5) and the fact that none of them had a survival endpoint or investigated a device, the low frequency of DSMB use in our pediatric trials may reflect a bias based on the type of studies included in the review.

Univariate logistic regression indicated that the highest proportion of variance (62%) is explained by the survival endpoint, followed by treatment duration (31%), treatment type (27%), and the country in which the trial was conducted (18%). These results support the significance of these predictors as suggested by the binomial and Fisher's exact tests. Taking into account the multicollinearity of the predictors (most of which are significantly correlated) and the use of univariate rather than multivariate logistic regression, the results should be interpreted with caution. The multicollinearity of the predictors indicates the involvement of a common factor: the associated level of risk. For example, trials investigating devices are considered high-risk since they use surgery, usually have survival as an end point, and are conducted only in the U.S.

Study Limitations and Future Directions

The main limitations of our study relate to the small number of trials reviewed, the involvement of only one research center, and only three categories for therapeutic area. Considering these limitations, future studies should include a larger number of trials, multiple research centers, and a broader distribution of therapeutic areas. Also, the sample should include enough studies for each predictor to statistically confirm the preliminary results. Additionally, increasing the sample size will allow better determination of the contribution of each predictor using multivariate logistic regression. Once these contributions are determined and evaluated for reasonableness, they can assist sponsors in making decisions about DSMB use.

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