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BRIEF REPORT

# To blind or not to blind first in human and exploratory clinical trials: Acceleration of development vs. risk of bias

**Sebastian Haertter**[1] | **Jitendar Kanodia**[2] | **Jack Cook**[3] | **Jeanette Alicea**[4] | **Bonnie J. Brennan**[5] | **Amit Desai**[6] | **Bela Patel**[7] | **Lin Pan**[8] | **Kosalaram Goteti**[9]

[1]Translational Medicine & Clinical Pharmacology, Boehringer-Ingelheim Pharma, Ingelheim, Germany

[2]Clinical and Translational Pharmacology, Theravance Biopharma US Inc., San Francisco, California, USA

[3]Clinical Pharmacology, Global Product Development, Pfizer Inc., Groton, Connecticut, USA

[4]Translational Medicine & Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut, USA

[5]Clinical Pharmacology, SBU Oncology, Bayer HealthCare Pharmaceuticals, Whippany, New Jersey, USA

[6]Clinical Pharmacology and Exploratory Development, Astellas Pharma Global Development, Inc., Northbrook, Illinois, USA

[7]Quantitative Pharmacology & Pharmacometrics (QP2), PPDM, Merck & Co., Inc., Kenilworth, New Jersey, USA

[8]Clinical Pharmacology, Genentech, Inc., South San Francisco, California, USA

[9]Quantitative Pharmacology, EMD Serono Research and Development Institute, Inc. (an affiliate of Merck KGaA, Darmstadt Germany), Billerica, Massachusetts, USA

**Correspondence**
Sebastian Haertter, Translational Medicine & Clinical Pharmacology, Boehringer-Ingelheim Pharma, Binger Strasse 173, 55216 Ingelheim, Germany.
Email: sebastian.haertter@boehringer-ingelheim.com

## Abstract

An IQ consortium working group (WG) conducted a survey across multiple biopharmaceutical companies to gain information about the level of blinding commonly utilized for early clinical development trials. The main objectives were: (1) to understand blinding practices between healthy volunteer (HV) and early explorative patient trials in all therapeutic areas except oncology where early clinical trials are commonly open-label; (2) to understand the rationale for blinding/unblinding practices; (3) to understand the groups and personnel involved in unblinding; and (4) strategic considerations around blinding/unblinding options in early clinical development trials—risk of bias vs. potential for acceleration. A survey containing 31 main questions with additional sub-clarifying questions was conducted. Sixteen large and mid-size pharmaceutical companies responded. Responses were aligned across functions within each participating company. Additional information was gathered at an American Association of Pharmaceutical Scientists (AAPS) webinar with polling options to roughly 550 registered attendees to evaluate the reason for the unblinding decisions. The results revealed divergence across companies in the blinding approaches most commonly applied but with some study types, there were clearly favored options. Based on these results, the WG developed strategic considerations for first-in-human HV trials and nonpivotal explorative trials in patients. This paper should facilitate discussions among various clinical development functions, such as Clinical Pharmacology, Statistics, Clinical, Bioanalytics, and Regulatory Functions. Such discussions on study design and operations are warranted to allow implementation of more flexible blinding approaches to accelerate data driven decisions in drug development and allow earlier access of patients to needful medicines.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Ambiguity in proper implementation of current guidances and inconsistency around unblinding nonpivotal trials in early clinical development exists amongst pharmaceutical companies. The unblinding approaches ranged from complete

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blinding of patient, investigator, and sponsor to whole sponsor team unblinded in healthy volunteer single ascending dose (SAD) or multiple ascending dose (MAD) trials and exploratory early studies in patients.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

Survey questionnaire and webinar polling questions reveal the current unblinding preferences across the industry in early clinical development trials for healthy volunteers and patients. The questions allowed to understand the strategy, rationale, and sponsor functions that are typically used for unblinding different types of trials.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

The results revealed some clearly favored options in terms of blinding investigator and sponsor functions depending on study type (SAD/MAD; proof of clinical concept/proof of pharmacologic principle vs. dose finding).

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

These findings may initiate discussions on the perceived risk of bias and provide more confidence in the opportunity to accelerate clinical development programs.

## INTRODUCTION

A need exists to accelerate and increase efficiency in drug development[1–3] so that resources can be allocated to projects with high likelihood of success.[4–7] Blinding is an important component of randomized, controlled clinical trials to reduce the risk of many types of bias: selection, performance, detection, and attritions.[8,9] The risk of bias is especially important for maintaining integrity, quality, and validity of confirmatory trials that support registration of a new drug.[10–12]

In the context of exploratory clinical trials in early drug development, where study objectives are primarily characterization of safety, tolerability, and pharmacology as opposed to clinical benefit-risk profile confirmation, there may be less impact and greater acceptance of the risk of bias as a reasonable trade off to enable rapid decision making. One way is to look at unblinded trial data while the trial is still running. Depending on how data are analyzed and disseminated, there is the potential to create bias or the perception of bias.[13,14] International Conference on Harmonization (ICH) E9 considers studies to be blinded if sponsors have adequate standard operating procedures to guard against inappropriate dissemination of treatment codes for staff required to be unblinded so long as they are not involved in the treatment or clinical evaluation,[15] however, it does not explicitly state examples beyond bioanalytical monitoring and safety. To understand industry practices related to blinding in early clinical trials and provide a commentary on considerations for optimal approaches, a working group was established under the auspices of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Clinical Pharmacology Leadership Group. A survey was developed to gain information about levels of blinding commonly utilized in early clinical trials. The results of the survey are presented and may enable development of a common understanding across various stakeholders in terms of feasibility of various options for blinding in early clinical trials.

## METHODS

Two surveys were conducted to gain information about design options for blinding commonly utilized for early clinical trials. The following types of studies were considered: single and multiple ascending dose (SAD/MAD) studies, nonpivotal proof of clinical concept (PoCC)/proof of pharmacologic principle (PoPP) studies, and dose finding studies. Oncology phase I and Clinical Pharmacology trials, such as drug-drug interaction, relative bioavailability/bioequivalence, or thorough QT trials were not considered as they are usually open label or follow a standard design. Information was separated for healthy volunteer and patient trials (Table 1). The first survey in IQ member companies included 31 questions in total on the assessment of the type of blinding used, the rationale of blinding or unblinding, what functions within a company were unblinded (if any), and when unblinding occurred.

Results of the initial survey were presented at an American Association of Pharmaceutical Sciences/IQ sponsored webinar.[16] During the webinar, participants were polled on the function they represented, their perceived risk of bias in SAD up to dose finding, and whether it was necessary to blind different types of data (Table S1). Additionally, participants were to

**TABLE 1** Results of a survey of IQ consortium companies and selected webinar survey items: Current practices and rationale for blinding in early healthy volunteer and patient trials

| Question | Response | Number of responses | |
|---|---|---|---|
| **Healthy volunteer studies (16 sponsors responded to SAD and MAD study questions)** | **Study type** | **SAD** | **MAD** |
| What is your rationale for (typically) blinding the investigator (check all that apply)? | Eliminates investigator bias | 12 | 14 |
| | Regulatory requirement | 1 | 1 |
| | Other: investigator not part of the sponsor trial team | 1 | 1 |
| | Other: eliminate selection bias | 0 | 1 |
| Do you report one or more of the following data types as mean and or individual (with individual data not linked to subject ID) back to investigator and consider blinding secured? | PK | Yes = 11 (85%) | Yes = 12 (86%) |
| | Safety | Yes = 9 (64%) | Yes = 10 (67%) |
| | PD | Yes = 6 (46%) | Yes = 7 (50%) |
| If PK/PD or PMx groups are unblinded, when are they unblinded? | Trial initiation | 6 | 6 |
| | Post randomization | 5 | 5 |
| | For defined analysis only | 3 | 3 |
| | Post dose escalation meeting | 1 | 1 |
| | Analysis submitted with dummy IDs | 1 | 1 |
| If PK/PD or PMx groups are unblinded, what is the rationale for unblinding? | Perform preliminary PK/PD analysis | 12 | 12 |
| | Facilitate faster decision making | 11 | 9 |
| | Assess outliers with respect to safety signals | 1 | 1 |
| | Determine PK for dose escalation | 1 | 1 |
| If bioanalytical groups are unblinded, when are they unblinded? | Trial initiation | 7 | 7 |
| | Post randomization | 5 | 5 |
| | For defined analysis only | 2 | 2 |
| If bioanalytical groups are unblinded, what is the rationale for unblinding? Are they unblinded? | Avoid placebo analysis | 11 | 11 |
| | Confirm correct dosing (e.g., analyze 2 post-dose samples in placebo subjects) | 1 | 1 |
| If statistical groups are unblinded, when are they unblinded? | Trial initiation | 5 | 5 |
| | Post randomization | 4 | 4 |
| | For defined analysis only | 5 | 5 |
| | Database lock | 1 | 1 |
| If statistical groups are unblinded, what is the rationale for unblinding? Are they unblinded? | Preliminary PK/PD | 8 | 8 |
| | Faster decisions | 1 | 1 |
| | Assess outliers with respect to safety signals | 5 | 5 |
| | Safety summaries | 1 | 1 |

| **Patient studies (14, 14, and 15 sponsors responded for PoPP, PoCC and dose finding study questions, respectively)** | **Study type** | **PoPP** | **PoCC** | **Dose finding** |
|---|---|---|---|---|
| What is your rationale for (typically) blinding the sponsor (check all that apply)? | Eliminates bias of investigator by sponsor | 6 | 7 | 14 |
| | Eliminates bias of sponsor decision making during the trial | 7 | 8 | 13 |

(continued)

**TABLE 1** (Continued)

| Patient studies (14, 14, and 15 sponsors responded for PoPP, PoCC and dose finding study questions, respectively) | Study type | PoPP | PoCC | Dose finding |
|---|---|---|---|---|
| | Subjective end points | 2 | 2 | 4 |
| | Regulatory requirement | 0 | 0 | 8 |
| | Easier process (1 database lock) | 0 | 1 | 1 |
| | Part of pivotal registrational package | 0 | 0 | 1 |
| What is your rationale for (typically) unblinding the sponsor (check all that apply)? | End points insusceptible to bias | 2 | 2 | 0 |
| | Minimizing accidental unblinding investigator (for specific functions unblinded vs. completely sponsor-open) | 4 | 3 | 2 |
| | Avoid premature discontinuation | 2 | 2 | 2 |
| | More rapid decision making | 7 | 6 | 3 |
| | Cost consideration | 2 | 2 | 1 |
| Do you report one or more of the following data types as mean to the investigator or sponsor and consider blinding secured? | To the investigator | | | |
| | PK | Yes = 3 (21%) | Yes = 4 (29%) | Yes = 3 (21%) |
| | Safety | Yes = 2 (14%) | Yes = 3 (21%) | Yes = 2 (14%) |
| | PD | Yes = 3 (21%) | Yes = 4 (29%) | Yes = 3 (21%) |
| | To the sponsor | | | |
| | PK | Yes = 8 (80%) | Yes = 8 (80%) | Yes = 4 (40%) |
| | Safety | Yes = 8 (80%) | Yes = 6 (60%) | Yes = 3 (30%) |
| | PD | Yes = 6 (60%) | Yes = 6 (60%) | Yes = 3 (30%) |
| If the sponsor is unblinded, what is the rationale for unblinding? | Certain functions unblinded | | | |
| | End points insusceptible to bias | 2 | 2 | 0 |
| | Minimizing accidental unblinding | 4 | 3 | 2 |
| | Avoid premature discontinuation | 2 | 2 | 2 |
| | More rapid decision making | 7 | 6 | 3 |
| | Cost consideration | 2 | 2 | 1 |
| | All functions unblinded | | | |
| | End points insusceptible to bias | 3 | 3 | 0 |
| | Minimizing accidental unblinding | 0 | 0 | 0 |
| | Avoid premature discontinuation | 0 | 0 | 0 |
| | More rapid decision making | 3 | 3 | 0 |
| | Cost consideration | 0 | 0 | 0 |
| If PK/PD or PMx groups are unblinded, when are they unblinded? | Trial initiation | 0 | 0 | 0 |
| | Post randomization | 3 | 3 | 3 |
| | For defined analysis only | 7 | 6 | 3 |
| If PK/PD or PMx groups are unblinded, what is the rationale for unblinding? | Perform preliminary PK-PD analysis | 10 | 10 | 5 |
| | Facilitate faster decision on dosing and following trials | 10 | 10 | 5 |
| If bioanalytical groups are unblinded, when are they unblinded? | Trial initiation | 4 | 4 | 0 |
| | Post randomization | 4 | 4 | 0 |
| | For defined analysis only | 2 | 2 | 2 |
| If bioanalytical groups are unblinded, what is the rationale for unblinding? | Avoid placebo analysis | 6 | 6 | 3 |

(continued)

**TABLE 1** (Continued)

| Patient studies (14, 14, and 15 sponsors responded for PoPP, PoCC and dose finding study questions, respectively) | Study type | PoPP | PoCC | Dose finding |
|---|---|---|---|---|
| If statistical groups are unblinded, when are they unblinded? | Trial initiation | 0 | 0 | 0 |
| | Post randomization | 1 | 1 | 0 |
| | For defined analysis only | 5 | 5 | 3 |
| If statistical groups are unblinded, what is the rationale for unblinding? Are they unblinded? | Preliminary PK/PD analysis | 5 | 3 | 0 |
| | To adapt trial design | 3 | 4 | 3 |
| | Futility analysis | 1 | 1 | 2 |
| **Webinar items** | | | | |
| After this webinar will you consider initiating a discussion with stakeholders on general blinding principles in particular on the option to allow certain sponsor functions access to unblinded data during the trial in the design of: SAD/MAD? | Yes | | | 24 (44.40%) |
| | No[a] | | | 27 (50.00%) |
| | No[b] | | | 3 (5.60%) |
| After this webinar, will you consider initiating a discussion with stakeholders on general blinding principles in particular on the option to allow certain sponsor functions access to unblinded data during the trial in the design of PoCC, PoPP and dose finding trials? | Yes | | | 20 (32.80%) |
| | Yes-but unlikely to change | | | 12 (19.70%) |
| | No[a] | | | 20 (32.80%) |
| | No[b] | | | 7 (11.50%) |

Abbreviations: ID, identification number; PK/PD, pharmacokinetic/pharmacodynamic; PMx, pharmacometrics; SAD/MAD, single ascending dose/multiple ascending dose; PoCC, proof of clinical concept; PoPP, proof of pharmacologic principle.

[a]Process already implemented with (certain) sponsor functions unblinded.

[b]Unlikely to change current approach of no access to unblinded data before data base lock.

appraise the information provided and then to strategically consider blinding and unblinding options in early clinical trials to determine whether the webinar might initiate a discussion within the company regarding the necessity of blinding explorative clinical studies (Table 1).

Survey results were collated and examined to understand the ranges in industry practice, rationale for blinding practices, and facilitate strategic consideration for blinding options in early clinical development.

## RESULTS

Sixteen IQ member companies responded to the first survey. Not all companies responded to every question. The number of respondents to the live webinar poll ranged from 54 to 123 depending on the question.

For the IQ member survey: SAD/MAD studies were always run with subjects blinded; PoPP, PoCC, and dose finding studies were always run with patients and investigators blinded. For the webinar survey, investigator and subject blinding status were not queried.

## Healthy volunteer studies

Based on IQ survey results, a wide range of blinding approaches are utilized by different sponsors for phase 1 SAD/MAD studies (Figure 1, upper panel, Table 1). On one end of the spectrum, 19% of the sponsors conducted SAD/MAD studies with all sponsor functions completely blinded. On the other end of the spectrum, 19% of sponsors conducted SAD studies and 12% of sponsors conducted MAD studies with all sponsor functions and the investigator unblinded (single blind). The majority of sponsors (56% of SAD and 63% for MAD) conducted these studies with certain sponsor functions unblinded during trial conduct.

Most sponsors consider reporting of individual and/or mean pharmacokinetic data (11/13 for SAD and 12/14 for MAD) and individual safety data (9/14 for SAD and 10/15 for MAD) without subject ID to maintain blinding. However,

only approximately half (6/13 for SAD and 7/14 for MAD) consider reporting of pharmacodynamic data. Only one sponsor considered blinding as a regulatory requirement.

Table 1 summarizes the timing of and rationale for unblinding various sponsor functions. Twelve of 14 sponsors unblind the bioanalyst, 11 of 16 sponsors unblind Clinical Pharmacology and pharmacometrics (PMx) functions, and 9 of 15 sponsors unblind the statistician by the time of dose randomization. Two sponsors of 14 unblind the bioanalyst, whereas 3 of 16 unblind the Clinical Pharmacology and PMx functions and 5 of 15 unblind the statistician for defined analysis only. One of the sponsors unblinds all the above functions post dose-escalation meeting while one sponsor unblinds only after database lock.

The key reasons for unblinding Clinical Pharmacology and PMx functions are to run preliminary analyses ($N = 12$ for SAD and MAD) that enable faster decision making ($N = 11$ for SAD and $N = 9$ for MAD). Statisticians are unblinded primarily for preliminary PK/PD analysis ($N = 8$ for SAD and MAD) or to evaluate outliers related to safety signals ($N = 5$ for SAD and MAD). Eleven of 12 sponsors unblind the bioanalyst to avoid placebo analysis while one sponsor also uses it to confirm correct dosing by spot checking placebo samples.

Based on webinar survey results (Table 1), 50% of the respondents indicated that certain sponsor functions are unblinded during conduct of SAD/MAD studies, including those (e.g., Clinical Pharmacology) involved in data evaluation. As a result of the webinar, 44% of respondents will consider initiating a discussion to allow certain sponsor functions to have access to unblinded data during SAD/MAD trials.

## Patients

Fourteen of 16 and 15 of 16 sponsors responded to the IQ survey for PoCC/PoPP and dose finding studies, respectively.

Blinding approaches utilized during patient studies are displayed in Figure 1. Results indicated that patients and investigators are always blinded. The extent of blinding of sponsors appeared to depend on the type of patient study (PoPP/PoCC vs. dose finding). In PoPP/PoCC studies, sponsors are unblinded 60% more often than in dose finding studies. Rather than to completely unblind all sponsor functions (7% of sponsor for both PoPP/PoCC and 6% for dose finding), a more common practice was to unblind certain sponsor functions. This practice, which was also dependent on study type, was over 80% more common in PoPP/PoCC studies compared with dose-finding studies.

Main reasons for sponsor blinding in patient studies is to eliminate investigator and sponsor bias in decision making (Table 1 and Table S1). Risk from bias was perceived as more important in dose finding studies versus PoPP/PoCC studies. Another leading rationale for sponsor blinding was attributed to a regulatory requirement (>50% of the time) for dose finding studies. In contrast, for PoPP/PoCC, regulatory requirements were not cited as a reason for sponsor blinding. It is interesting to note, that when asked about the types of comments received from regulatory agencies regarding blinding, the only response was that "No comments regarding blinding have ever been received," regardless of study type. Other less frequent justifications for sponsor blinding included subjective end points, easier process, and part of the pivotal registration package.

The leading rationale for sponsor unblinding in patient studies is to allow for more rapid decision making. Other less frequent justifications for sponsor unblinding included cost consideration and to avoid premature patient discontinuation from studies. End point insusceptibility to bias was a reason for sponsor unblinding in PoPP/PoCC studies for 25% of respondents but never in dose finding. Furthermore, when looking at the rationale for unblinding by sponsor functions variability was evident (Table 1 and Table S1). For Clinical Pharmacology/PMx, the use of unblinding is for rapid decision making through conducting preliminary PK/PD analysis as well as for faster decisions on dosing and future trials. For bioanalysis functions, unblinding is to avoid placebo analysis; (PoPP/PoCC studies: ~65%; dose finding studies: ~35% of respondents). For biostatistics, unblinding rationale were mostly due to trial design adaption but were also considered for conducting preliminary PK/PD analysis and futility analysis.

With regard to the timing of unblinding, the bioanalytical function tends to be unblinded earliest, during trial initiation, with subsequent unblinding of Clinical Pharmacology/PMx and Biostatistics.

Based on webinar survey results (Table S1), ~33% of the respondents indicated that they already unblind certain sponsor functions in their PoCC/PoPP studies. Another 33% of the respondents will consider initiating a discussion on the option to allow certain sponsor functions access to unblinded data during PoCC/PoPP trials. Small number of respondents (~3%) indicated it would be unlikely to change current approach of no access to unblinded data before data base lock.

## DISCUSSION

Current regulation based on ICH E9 has a definition of double blind[15] but none for clinical evaluation (related to patient examination or any evaluation of data?). Further, the examples of sponsor staff given do not

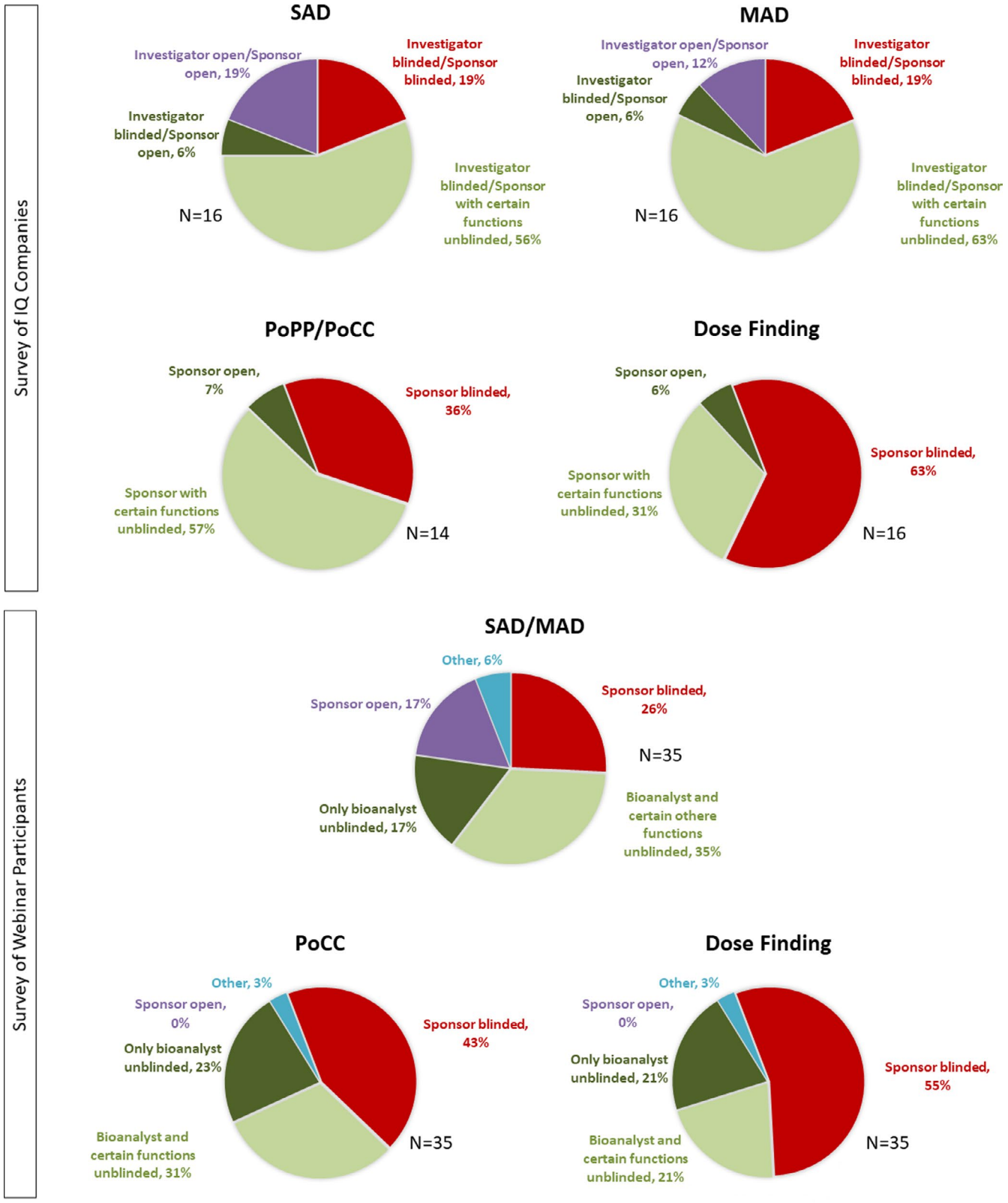


**FIGURE 1** Typical study designs for various study types from companies within the IQ consortium (upper panels) and webinar (lower panels) surveys. The *N* represents the number of respondents to these survey questions. For IQ companies survey: SAD and MAD studies were always run with subjects blinded; PoPP, PoCC, and dose finding studies were always run with patients and investigators blinded. For the webinar survey, investigator and subject blinding status were not queried. MAD, multiple ascending dose; PoCC, proof of clinical concept; PoPP, proof of pharmacologic principle; SAD, single ascending dose

include functions included in quantitative evaluation of end points (Clin Pharm, Pharmacometrics, Statistics, and Data Manager) and thus leads to variable interpretation of the guidance across companies. Although most statisticians consider subject, investigator, and sponsor blinded as the best possible approach to avoid bias, this survey demonstrated that companies try to implement processes in early double-blind patient trials (phase Ic or phase IIa) allowing sponsor functions mentioned above that are involved in the analysis of end points, access to unblinded data during the trial while preserving the patient and investigator blind. Operationally, these trials may be more complex but they provide the opportunity of acceleration in the development or early termination of a project.

Trial design options for SAD/MAD, and in particular the value of double-blind designs and placebo treatment in healthy volunteer studies, has been discussed previously.[17–19] However, this survey extends the scope to explorative patient trials with the aim to demonstrate PoCC and dose finding with a focus on the question of blinding. As clinical development progresses, with the dose finding trials being quite decisive for confirmatory phase III trial, companies tended to be more stringent in terms of blinding, perceiving a higher risk of bias. The option of blinded sponsor was less frequently applied to SAD and MAD trials in healthy volunteers as well as PoPP and PoCC studies. In these cases, unblinded data access during the trial was allowed to certain sponsor functions or even the whole sponsor team, hence, potentially contradicting the notion that the unblinded staff should not be involved in the treatment or clinical evaluation.[15] Regulatory agencies consider studies to be adequately blinded even when certain sponsor functions are unblinded so long as the sponsor has established adequate standard operating procedures to guard against inappropriate dissemination of treatment codes.[15] However, the surveys did not ask on potential "safeguards" to prevent bias such as separate staff (Statistics, Clinical Pharmacology, and Pharmacometrics) outside the trial team. The surveys did have further limitations, as responses were almost exclusively from large pharmaceutical companies, some responses (fully sponsor-open patient trials) could not be clarified as well as some surprising and unexplained discrepancies between PoPP and PoCC settings within one company. Responses may have been influenced by portfolio and some responses may have been missing or incomplete limiting the data collected and data interpretation.

Even with the above limitations, it seems justified to draw the conclusion that it is a valuable option to allow at least certain sponsor functions access to unblinded data during the trial conduct across all exploratory study types from SAD to dose finding, even functions involved in the clinical evaluation, such as Clinical Pharmacology or Pharmacometrics. Accordingly, whenever unblinding of certain sponsor functions during trial conduct was used, no respondent reported that regulators raised doubts about the validity of the trial.

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## CONFLICT OF INTEREST

J.C. is an employee of Pfizer, Inc. S.H. and J.A. are employees of Boehringer Ingelheim. L.P. is an employee of Genentech, Inc. J.K. is an employee of Theravance. B.P. is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. K.G. is an employee of EMD Serono Research and Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt Germany); B.B. is an employee of Bayer HealthCare. All other authors declared no competing interests for this work.

## AUTHOR CONTRIBUTIONS

S.H., K.G., J.K., J.A., J.C., L.P., B.B., B.P. and A.D. wrote the manuscript. S.H., J.K., J.A., J.C., A.D., B.B., and K.G. designed the research. S.H., K.G., J.K., J.A., B.B., and J.C. performed the research. K.G., A.D., J.C., J.K., L.P., and B.P. analyzed the data.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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