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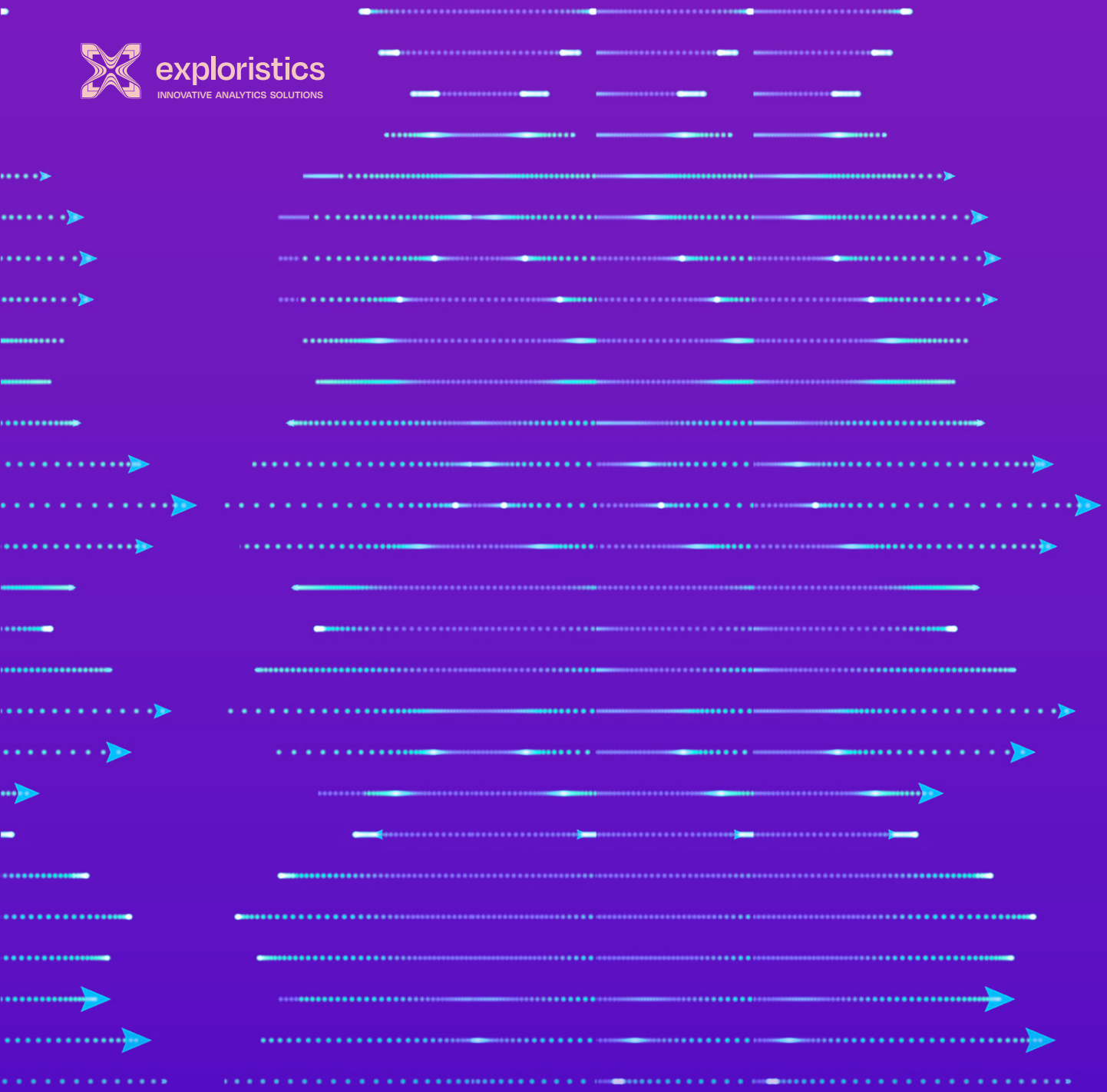
INNOVATIVE ANALYTICS SOLUTIONS



Whitepaper

Estimands – Opportunity or Risk for drug developers?

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The word "Estimand" is one that has been gaining use and influence within medicine development over the last few years, but which still holds some mystery for many people. In this paper we explain what you need to know regardless of your role or specialism: the rationale behind the estimand framework, clarify the definitions, and summarise the impact they could have for your next trial.

The historical gold standard

Everyone working on randomised clinical trials is very familiar with the intent-to-treat (ITT) principle as the "gold standard" for interpretation of results – i.e., that all randomised subjects, regardless of adherence to the protocol, are included in the analysis and are considered as belonging to the treatment arm to which they were randomly assigned. This avoids biases which may emerge if participants withdraw from the trial in an unbalanced way (e.g., due to side-effects). However, in practice analysts will often have to make a (subjective) decision how to include subjects who have missing data as a result of withdrawal before the key timepoint of interest. Historically, imputation approaches such as last observation carried forward (LOCF) would have been used to fill in missing data, as shown in Figure 1. This would be supported by alternative populations for analysis such as "per protocol" (PP) which only includes subjects following the planned design and having a measurement taken at the primary timepoint. Although both approaches can introduce biases for different reasons, for many years these methods were considered sufficient to provide a robust interpretation if they broadly gave the same conclusion.

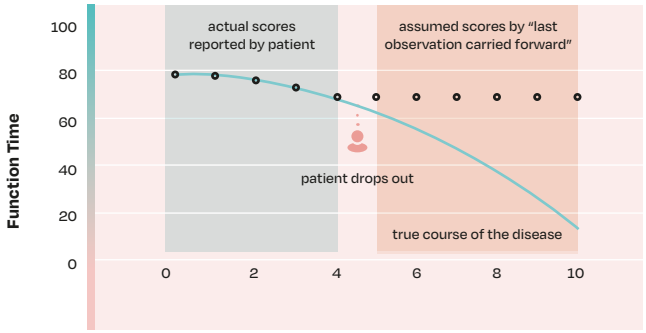

Figure 1. Potential bias introduced by imputation strategy last observation carried forward (LOCF).

Creating a new standard with clarity

Nearly 10 years ago the ICH steering committee recognised that guidance for industry was required to bring consistency and clarity to the handling of missing data in ITT analysis, and further to address another issue that was equally important as a potential source of bias but less recognised by researchers and analysts – that of non-missing data which had been impacted by events occurring during the trial as shown in Figure 2 (e.g., taking a medication which could positively or negatively affect the primary endpoint). A working group was established, which ultimately delivered the ICH E9 (R1) addendum on Estimands in 2019 [1].

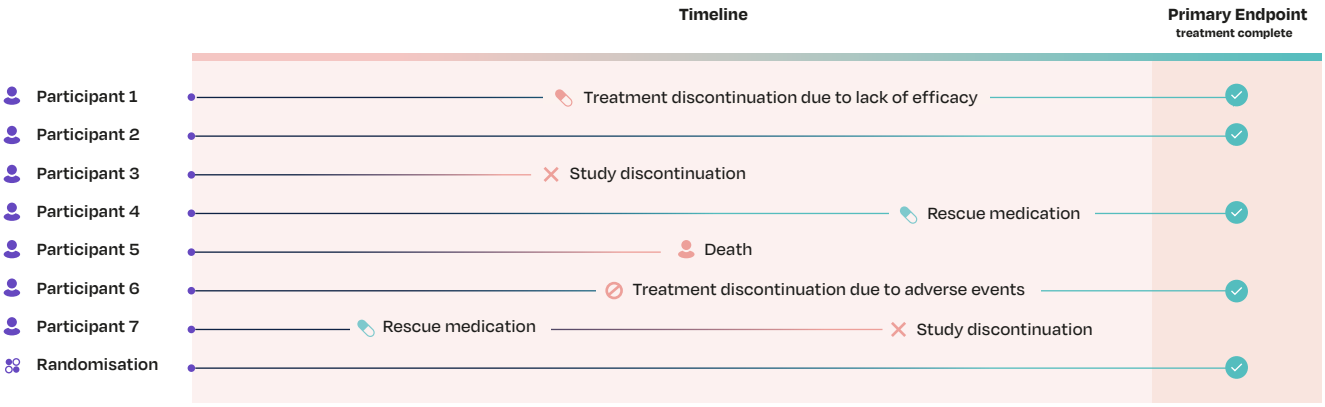

Figure 2. Events that can occur during a clinical trial that may affect the primary endpoint.

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Aims of the current guidance on estimands

The guidance in ICH E9 (R1) defines an **estimand** as a precise description of the treatment effect reflecting the clinical question posed by the trial objective, or in short ***what is to be estimated***. The estimator is the pragmatic partner of the estimand, defining ***how the treatment effect will be estimated***. The aim of the guidance is to enable clinical researchers to reach better alignment between study objectives, design, data collection, analysis and interpretation. This will be achieved because the requirement for a clearly stated set of estimands in the protocol encourages conversations within study teams between medics, statisticians and operational colleagues, as well as between sponsors and regulators.

Understanding key terms within the estimand framework

There are several terms introduced within the estimand framework with specific and nuanced meanings which are important to define and understand.

Definitions

Intercurrent events (ICEs) are events that occur after treatment initiation and affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Multiple ICEs are likely within a trial and potentially for the same participant. The approach to ICEs through study conduct, data handling and analysis is the essence of defining an estimand.

A **strategy** reflects the choices made on how to address ICEs, in order to best describe the treatment effect that is targeted. Five strategies are given names within the guidance for ease of reference, but their use is not mandatory, and the key is clarity at the design stage. Table 1 is developed from the ICH E9(R1) Training Material [2] and gives the definitions of the strategies, together with examples.

Table 1. Strategies for addressing intercurrent events when defining the clinical question of interest.

Strategy	Description	Examples
Treatment Policy	Occurrence or otherwise of ICE is irrelevant in defining treatment effect of interest.	When specifying addressing rescue medication as an ICE, ICE occurrence is ignored, and observations collected after rescue are used for the variable of interest.
Hypothetical	Hypothetical scenario in which ICE would not occur (should be explicitly stated and justified).	When rescue medication must be made available for ethical reasons, a treatment effect of interest might concern outcomes if rescue unavailable (e.g., in a region with a different regulatory regime).
Composite	Occurrence of ICE is informative about treatment effect and so is incorporated in endpoint (useful for terminal events e.g., death).	If a patient dies or takes rescue medication it may be considered that the allocated treatment was not effective, and the patient was not successfully treated, so if the outcome is: • binary success/failure, use of rescue would dictate treatment failure. • measured in a scale or score, subjects experiencing ICE could be given "bad" value.
While on Treatment	The response to treatment prior to the occurrence of the ICE is of interest.	Subjects may discontinue treatment due to e.g., death, yet it is of interest to: • measure treatment success based on effect on symptoms before death. • assess risk of an adverse drug reaction during period of adherence to treatment.
Principal Stratum	Interest is in treatment effect within a patient subpopulation in which an ICE would/would not occur.	Interest is in treatment effect: • on severity of infections in the principal stratum of patients becoming infected after vaccination. • among patients who can tolerate a toxic test treatment.

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Each of the five strategies outlined by the guidance for dealing with ICEs will have implications for the study design with regard to study conduct, data handling and analysis from an operational and statistical analysis perspective. These are shown in Table 2.

Table 2. Implications on study design of the five different strategies that can be used to address ICEs

Strategy	Implications for study conduct, data handling and analysis
Treatment Policy	• Requires data to be collected after the ICE and/or an assumption that missing data after the ICE are MAR/uninformative and using a corresponding analysis (e.g., MMRM, MI or Cox PH model). • In general, cannot be used for terminal events because data do not exist and uninformative missingness assumption cannot be justified.
Hypothetical	• May require an algorithm or predictive model aligned with the hypothesised scenario to explicitly impute values not observed. • Alternatively requires an assumption that unobserved data after the ICE would follow the same distribution as observed data (and so are MAR/uninformative) and using a corresponding analysis (e.g., MMRM, MI or Cox PH model).
Composite	• By construction, all subjects will have an outcome for the composite endpoint. • Established analysis methods for binary and time-to-event variables can be applied (logistic or Cox PH regression, CMH test, etc). • Standard analyses of continuous data (linear regression, MMRM) may be sensitive to the imputed "bad" value, and so less standard analyses estimating a trimmed mean or median may be considered for greater robustness.
While on Treatment	• Data for analysis may be the same as for the hypothetical strategy, but the variable and/or population level summary will be different. • Analysis may use the last available measurement prior to the ICE (similar to traditional LOCF approaches), or the average prior to the ICE. • Alternatively, analysis may focus on a slope or rate (e.g., mixed model with time fitted as a continuous variable or negative binomial regression with an exposure time variable)
Principal Stratum	• Subjects who experience an ICE on the test treatment will often be a different subset from those who experience the same ICE on the control. • The significant challenge of analysis to estimate effects in principal strata is that strata membership is unknowable from the data from a parallel group study. • Collection of covariates which can help predict ICEs and outcomes is important. • Estimation of effects within principal strata relies on strong assumptions so complex analyses are typically required (MI, Bayesian mixture models).

Abbreviations: CMH: Cochran-Mantel-Haenszel, LOFC: last observation carried forward, MAR: Missing at random, MI: Multiple imputation, MMRM: Mixed model for repeated measure.

Attributes

There are five attributes of an estimand: **treatment**, **population**, **variable**, **ICEs** and **population-level summary**, as shown in Figure 3. These attributes are outlined in more detail in Table 3, which also includes information on how these attributes interact with each other (particularly ICE strategies).

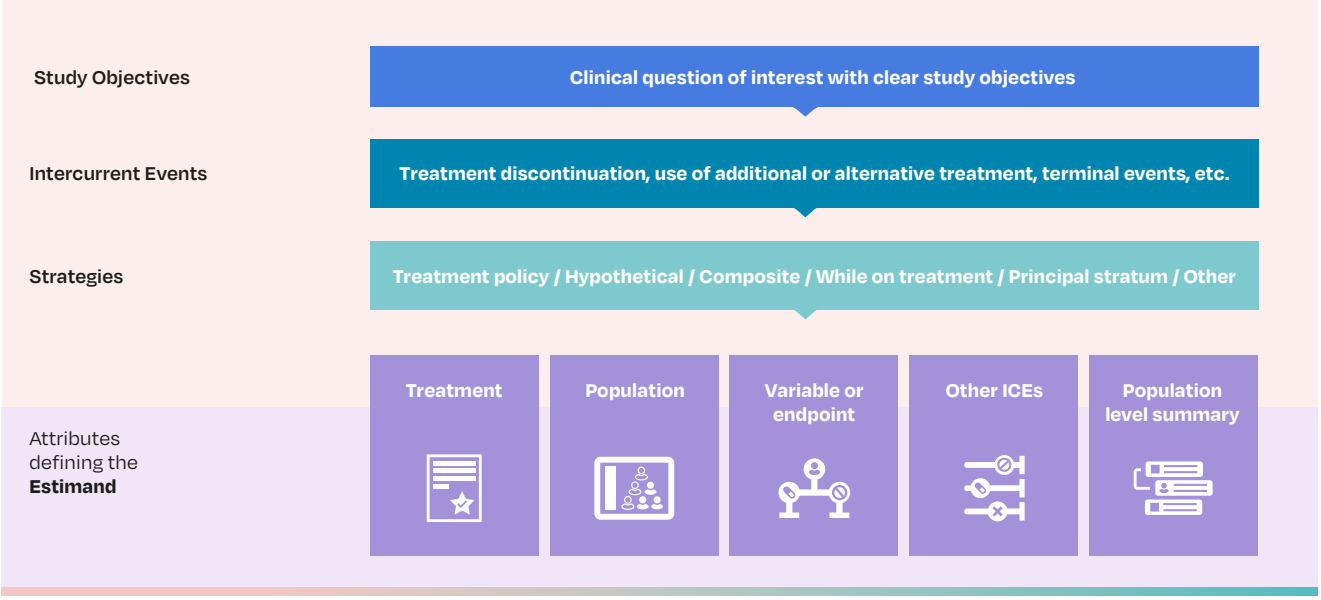

Figure 3. The five estimand attributes required to specify an estimand, and the steps needed to define them.

Analysis types

The guidance distinguishes **sensitivity analysis**, i.e., those targeting the same estimand as the main estimator to explore the robustness of inferences to deviations from underlying assumptions, from **supplementary analysis** i.e., targeting a different estimand to provide additional insights for interpretation of trial results. It is important to differentiate between the two, as they have distinct statistical meanings but are often used interchangeably which can be misleading.

Opportunities arising from the estimand framework

There are obvious opportunities to use the estimands framework to improve the clarity of development plans and protocols, and hence improve the clinical research that we conduct. These include:

- **a shared common understanding up front between sponsors and regulators** which should lead to agreement on the most relevant estimates of treatment effects for licensing and prescribing decisions, and hence less uncertainty for sponsors at the time of regulatory assessment.
- **an increase in the transparency of research objectives with other stakeholders**, such as current or future investors, patient groups or the wider public. The expectation is on the sponsor to invest the time and thought in trial design upfront, in order for these benefits to be realised later.
- **aligning objectives with estimands allows researchers to fully align all aspects of study design** more confidently. This includes ensuring that all the relevant data is collected to allow the desired objective to be optimally assessed, and that statistical analyses can provide reliable and valid estimators for inference. Collecting data from subjects after they withdraw from treatment will become more commonplace.

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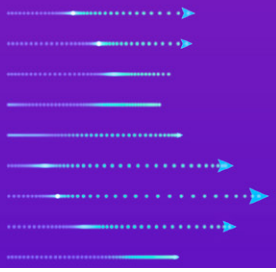
Table 3. The five estimand attributes and their interactions.

Strategy	Description	Examples	Interaction with other attributes
Treatment	Treatment condition of interest and alternative treatment to which a comparison will be made.	• Individual interventions (e.g., test drug, medical device, health intervention, etc.) • Combinations of interventions administered concomitantly (e.g., as add-on to standard of care, or a regiment including a sequence of interventions • Allowed rescue treatments and changes in background medications	• If variations to the specified treatments are to be considered ICEs, this should be clearly specified in this attribute (e.g., use of rescue, changes in background treatments)
Population	Patients targeted by the clinical question.	• The whole trial population • A subgroup defined by a particular characteristic measured at baseline • A principal stratum	• A principal stratum (or strata) could be defined by the occurrence (or non-occurrence) of an ICE
Variable (or endpoint)	Variable (or endpoint) to be obtained for each patient in order to address the clinical question of interest.	• A continuous or categorical clinical measurement to be taken at a specified timepoint • A binary clinical assessment to be made at a specified timepoint • A clinical event for which the time to occurrence is of interest	• The specification of the variable may include whether the patient experiences an ICE. **For example:** • using composites (e.g., treatment failure defined as non-response or treatment discontinuation) • using measurements taken prior to discontinuation of treatment (e.g., ccurrence of an adverse drug reaction while exposed to treatment)
Other ICEs	Any other ICEs that have not yet been reflected in the specification of treatment, population or variable.	• Missed doses or treatment modifications for reasons unrelated to intervention in the trial • Missed assessments or study withdrawal for reasons unrelated to the intervention	Common ICEs will usually be accounted for: • as part of the treatment of interest or alternative treatment (treatment policy strategy, hypothetical strategy) • as part of the population (principal stratification strategy) • as part of the variable (composite strategy, while on treatment strategy) • Any other ICE will usually be reflected using treatment policy, hypothetical or while on treatment strategies
Population-level summary	Provides a basis for comparison between treatment conditions.	• A mean, median or trimmed mean • A proportion • A hazard rate • A rate • A difference in means, medians or trimmed means • A difference or ratio of proportions • A hazard ratio, t-year event-rate difference or restricted mean survival time difference • A difference or ratio of rates	• Data for analysis may be the same for the hypothetical and while on treatment strategies but the variable and/or population level summary will be different



Potential risks associated with the estimand framework

The explicit acknowledgement within the estimands framework that different stakeholders will be interested in different estimands is very much to be welcomed, allowing a protocol to prospectively plan analyses focused on all perspectives from patients, clinicians, regulators and payers. However, there is a risk in doing so that studies may have to become larger, increasing development costs for sponsors and extending development times for everyone. This is because regulators are seeing the new guidance as a chance to reset expectations in terms of statistical analysis approaches, with old-fashioned ITT with LOCF and PP no longer sufficient. Composite strategies for intercurrent events are likely to become more common as the primary estimand, which typically require larger sample-sizes to achieve sufficient power.

Another effect of estimands which will potentially increase trial size is that the number of unknown factors at the design stage is more apparent – not just treatment effect and variability, but also rates of ICEs such as treatment-related adverse events, withdrawal or non-compliance due to treatment, etc. The probability of success will depend on these unknown rates, and the risk associated with an unexpected result must be managed. If "bad luck" on any unknown factor could lead to study failure, bigger trials will be needed to protect against more unknown factors.

Beyond study size, the estimand framework brings practical costs to sponsors in that they must allow sufficient time at the design stage for alignment within the study team, engagement with external experts and reaching agreement (or not) with reviewers such as regulators. However, while the potential risks outlined should be considered, not considering estimands potentially leaves developers open to a series of greater risks including:

- **increased timelines** to try and align study objectives with design retrospectively,
- **regulators not approving plans or requesting amendments** in line with their guidance
- **not thinking about estimands in early phase studies** and so getting a biased view of how good the treatment is.

This can have expensive repercussions if late-stage programmes are based on biased estimates, increasing the risk of failure.

Evaluating estimands early improves study design and outcomes

On balance, the benefits of using the estimand framework far outweigh any potential risks involved. One of the biggest risks to any study in any phase of development is that the design is not aligned with the study objectives, and so will not answer the question you think you are answering. Use of the framework should prevent this. Moreover, while not mandated, considering estimand strategies is now actively encouraged by regulators to improve study outcomes. Therefore, it is incumbent on developers to integrate use of the framework into their design approach to ensure successful regulatory interactions.

This leads to the final opportunity – one for statisticians and quantitatively-minded researchers to grasp. Traditional sample-size calculations do not accommodate ICEs in the calculation of power, and the use of simulation of subject-level data at the design stage, incorporating the different estimand strategies as a design factor, will have to become more widespread. Earlier engagement with statisticians on study design will be needed here. However, this will allow quantification of the impact of different estimand and analysis choices on the probability of success – allowing efficiencies to be identified where they exist, and otherwise providing greater confidence that the planned sample-sizes bring benefits of reduced risk of failure both at the analysis and regulatory review stages.

At Exploristics, we provide a uniquely targeted approach to the design of clinical studies including the evaluation of estimand strategies using simulation techniques. In this way, we ensure that study objectives can be achieved with the most suitable study design so that the **right data**, is collected in the **right patients**, in the **right way**. This benefits not only developers in terms of development timelines and costs, but most importantly the patients in need of new treatments.

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has over 20 years' experience as a statistician in the pharmaceutical industry and is Head of **Strategic Consulting** at Exploristics. Sam has co-authored over 50 articles in edical and statistical publications and has extensive expertise in experimental medicine, adaptive designs and the application of Bayesian approaches to clinical trial design and analysis.

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About Exploristics

Exploristics is a global provider of state-of-the-art software and biostatistics services to the life sciences sector. We offer key support to organisations involved in the clinical development of new healthcare breakthroughs with our strategic consultancy expertise and flagship simulation software, **KerusCloud**.

For more information on Strategic Consulting and Biostatistics Services please contact VP of Sales & Marketing Abbas Shivji at abbas.shivji@exploristics.com.

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