Frequently Asked Questions

A) Systematic review

What is Systematic review?

"A systematic review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. The conduct of systematic reviews uses explicit methods aimed at minimizing bias, in order to produce more reliable findings that can be used to inform decision making" (Cochrane, 2014).

Where is it used in the life cycle and by who

Healthcare professionals and policy makers conduct systematic reviews using explicit methods aimed at minimizing bias, in order to produce more reliable findings that can be used to inform decision making, such as the validity and verifiability of numerous clinical studies to identify if a therapeutic is truly efficacious.

It is used every time is necessary to appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question.

Why you should be using it

It should be used for the following reasons:

- Increase the and optimize the value of your innovations by identifying numerous applications of your innovation, based on published preclinical and clinical data and inform your strategy and plans for where, when and how to develop them.
- Ensure that your R&D&I is relevant, and you can identify the stakeholders, advisory groups and user groups linked to your innovations
- Exhaustive searches are undertaken to find as much as possible of the relevant research. It reduces bias in fact conclusions are not overly influenced by the most accessible research. A 'protocol' sets out how the systematic review is to be conducted before the work starts. It reduces bias because procedures cannot be overly influenced by results. Systematic reviews are transparent about how their conclusions are generated because it avoids misrepresentation of the knowledge base, in fact each piece of research is evaluated and its quality and relevance made clear;
- The systematic review methods are made explicit: users of the review know if they can trust the review's findings because readers can judge how well it has been done.
- The findings of sound research are synthesized to produce clear and easily accessible messages about the reliable evidence available on a given topic. This is done appraising individual studies and pooling their results means conclusions can be drawn about the direction of the evidence as a whole.

B) Meta analysis

What is Meta Analysis?

A subset of systematic reviews; a method for systematically combining pertinent qualitative and quantitative study data from several selected studies to develop a single conclusion that has greater statistical power. This conclusion is statistically stronger than the analysis of any single study, due to increased numbers of subjects, greater diversity among subjects, or accumulated effects and results.

Where is it used in the life cycle and by who

Meta-analysis would be used by healthcare professionals and policy makers for the following purposes:

- To develop a more correct estimate of effect magnitude.
- To establish statistical significance with studies having conflicting results.
- To provide a more complex analysis of harms, safety data, and benefits.
- To examine subgroups with individual numbers which are not statistically significant.

Why you should be using it

The use of a meta-analysis permits and guarantees:

- Better definition of your target or the target you should be aiming for early in your preclinical and experimental work
- Increased identification of your precise patient population and beneficiaries
- Delineation of the anticipated primary endpoints of future clinical studies and reverse engineering of this information to the preclinical study design, to generate a stronger dossier
- Greater statistical power:
- Confirmatory data analysis:
- Greater ability to extrapolate to general population affected
- Having an evidence-based resource.

C) Early Health Technology Assessment (HTA)/market access scientific advice and market access planning and execution

What is HTA?

The mounting concerns regarding the growing gap between demand for health services and available resources has long created the need to regulate healthcare expenditure and governments have increasingly introduced formal systems to assess the value for money of health care technologies coming to market.[i] The predominant processes to do so are Health Technology Assessments (HTAs).

Where is it used in the life cycle and by who

- HTAs serve the purpose to assess a products value for money to inform decisions about whether to fund health care technologies both on a national level as well as subnational levels.
- HTAs take place at time of marketing authorisation but can take place earlier. They are normally initiated earlier and preparations for high quality HTA submissions can take up to two years.
- Besides of the preparations for HTA submissions it is important to generate high quality evidence to inform and support submissions and subsequent discussions with payers. Therefore, it is important to take into account HTA considerations when designing pivotal clinical trials, especially phase 3 licensing studies. Such considerations can be done through official procedures with regulatory and HTA organisations as well as through informal procedures like advisory board meetings or one-to-one interactions with experts. Dependent on the procedure this can take up to half a year from first engagement with the procedure with further time needed prior for preparations.

Why you should be using it

- HTA advice helps you prepare for HTAs and subsequent discussions with payers to enable market access.
- High quality preparation for HTAs and discussions with payers improves chances of success to gain reimbursement and enable market access.

D) Study design and sample size calculation for observational epidemiological study and randomized clinical trials

What is Study design and sample size calculation?

Clinical study design is the formulation of trials and experiments, as well as observational studies in medical, clinical and other types of research (e.g., epidemiological) involving human beings. The goal of a clinical study is to assess the safety, efficacy, and / or the mechanism of action of an investigational medicinal product or procedure, or new drug or device that is in development, but potentially not yet approved by a health authority (e.g. AIFA, EMA). It can also be to investigate a drug, device or procedure that has already been approved but is still in need of further investigation, typically with respect to long-term effects or cost-effectiveness.

One of the pivotal aspects of planning a clinical study is the calculation of the sample size. It is naturally neither practical nor feasible to study the whole population in any study. Hence, a set of participants is selected from the population, which is less in number (size) but adequately represents the population from which it is drawn so that true inferences about the population can be made from the results obtained.

Referring to pilot studies and previous research studies, we can choose a proper hypothesis and simplify the studies by using several software tools which implemented procedures for the sample size calculation. The study protocol has to include a section regarding the sample size calculation.

Where is it used in the life cycle and by who

Calculation of the sample size is carried out during the planning stage. Thus, calculating the sample size is usually conducted in prospective random control studies. Retrospective studies use statistical power rather than the calculation of sample sizes and we call these 'post hoc power analyses'. Also, because researchers expect to uncover findings by referring to previous research studies or pilot studies, the calculation of sample size is done after references are investigated, and before the full-scale research begins. Moreover an accurate sample size calculation is also a necessary requirement for regulatory submission.

Why you should be using it

Calculating the sample size is essential to reduce the cost of a study and to prove the hypothesis effectively. Many researchers want to show that the two groups are truly distinct, but they will fail to find significant differences if the sample size is not big enough. Also, they can waste time and money by continuing an investigation past the time it needs to be continued because they do not know when the testing has been completed since they haven't calculated the sample size before the investigation begins. If the sample size is already large enough to prove that the experimental group is superior, maintaining treatment for the control group could be an ethical problem because the treatment they are receiving is obviously inferior. Thus, it is clear that calculation of sample size is essential ethically and also effectively to get the greatest satisfaction at the lowest cost.

E) Statistical analysis : predictive inference and statistical modelling

What is it?

Statistical analysis includes all statistical methods to be used for demonstrating the achievement of the primary, secondary and all other endpoints of the study. These methods can include parametric e non parametric test for the comparison between treatment arms and statistical modeling to estimate the effect of the treatments on the endpoints of interest. Depending on the type of endpoints (continuous, categorical, time to event) a different analysis strategy can be used (linear regression, logistic regression, survival analysis…). Methodology for imputation of missing data and different strategies fro performing sensitivity analysis can be also included.

Where is it used in the life cycle and by who

The statistical analysis used to verify a treatment effect should be clearly described in the study protocol and then, in more detail, in the SAP. In general, the main statistical analysis should be made for each of the efficacy, safety, and usefulness evaluations. As for the main statistical analysis, the statistical hypothesis and analytical technique suitable for its verification should be selected beforehand and described, together with the analysis items. The biostatistician is responsible for the statistical analysis definition.

Why you should be using it

The use of statistical analysis allows clinical researchers to draw reasonable and accurate inferences from collected information and to make sound decisions in the presence of uncertainty. Mastery of statistical concepts can prevent numerous errors and biases in medical research. Accurate, detailed and sophisticated statistical analysis is a fundamental requirement for regulatory submission.

F) Study Protocol and SAP

What is Study Protocol and SAP?

Study Protocol: A Study Protocol for a clinical trial is a study plan, designed to describe objectives, background, methodology, organization, the participants, interventional procedures and assessment tools of the trial. The protocol is the 'operating manual' for the clinical trial, and ensures that researchers (especially in multicenter trials) all perform the trial in the same way on patients with the same characteristics.

SAP: A SAP (Statistical Analysis Plan) is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.
It should be reviewed and possibly updated as a result of the blind review of the data and should be finalized before breaking the blind. If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review. Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

Where is it used in the life cycle and by who

Study Protocol and SAP are documents required by ethical committee and regulatory agency to conduct a clinical trial according GCP (Good Clinical Practice), especially when the purpose is obtaining an approval.

Why you should be using it

These documents are necessary in order to conduct clinical research according to GCP (Good Clinical Practice), an international quality standard provided by International Conference on Harmonization (ICH), an international body that defines standards, which governments can use to regulate clinical trials involving human subjects.

The use of a pre-specified study protocol:

- creates an incentive to understand the biological function of the intervention;
- carefully define the population of interest, target the most appropriate end points, and achieve certainty about the statistical approach;
- carefully define hypotheses and minimal testing means that standard errors and P values are accurate measures of uncertainty and statistical evidence is rigorous;
- a study protocol can also be referred to and reviewed to understand the questions, end points, and subgroup analyses that were defined ahead of time and those that were post hoc and in need of replication for validation.

The use of a pre-specified SAP:

- promotes good planning rather than haphazard data analysis and communicates this distinction to reviewers and readers;
- optimizes statistical resources to focus the best methods on good questions, those with the potential for important findings, either negative or positive. When key hypothesis are defined at the outset, they can be carefully addressed;
- facilitates transparency. The submission of an SAP provides reviewers with a complete description of what was done;
- increases efficiency by avoiding distracting messages, maintaining focus on the a priori hypotheses with room for post hoc and sensitivity analysis to be reported.

G) Value dossiers

What is a value dossier?

- A Value Dossier presents a summary of the clinical, economic, and humanistic value and supporting evidence for a product in a disease area as well as background information on that disease (i.e., burden of illness, epidemiology, etc.).
- Value dossiers compile evidence about healthcare interventions for purposes of internal communication and to support submissions to HTA organisations, as well as national and local payers.

Where is it used in the life cycle and by who

- A core, or Global, value dossier should be available at time of marketing authorisation to support submissions to HTA organisations.
- Updates should be made available as new data becomes available and to tailor messages further to sub-national payers.

Why you should be using it

- To help communicate your products value to national and sub-national payers to gain reimbursement and enable market access.

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[i] Sorenson C, Chevreul K, Durand-Zaleski I. The Rise of Health Technology Assessment in Europe: Looking Back and Looking Forward. Paper prepared for the 10th anniversary meeting of the European Health Policy Group London School of Economics and Political Science, 16-17 September 2010. https://www.jiscmail.ac.uk/cgi-bin/webadmin?A3=ind1009&L=EHPG&E=base64&P=7598620&B=------_%3D_NextPart_001_01CB4F9C.FBB9526C&T=application%2Foctet-stream;%20name=%22The%20Rise%20of%20Health%20Technology%20Assessment%20in%20Europe_EHPG_Sorenson%20et%20al..pdf%22&N=The%20Rise%20of%20Health%20Technology%20Assessment%20in%20Europe_EHPG_Sorenson%20et%20al..pdf&attachment=q&XSS=3 (accessed: June 21st, 2017)