

MANAGING TIME & RISK – REMEMBER MURPHY AND HOFSTADTER

EARLY PHASE CLINICAL TRIALS – MAXIM #4



Early phase clinical trial protocols tend to become more and more complex, focusing on gaining as much scientific insight as possible. Multiple objectives are embedded into one single design. Today, in addition to safety assessments and pharmacokinetic (PK) sampling, pharmacodynamic (PD) read-outs are nowadays implemented as standard in phase 1 protocols. These PD

assessments can come in different forms: blood or other body fluid samples followed by special assays, imaging or specific functional testing.

As a result, time critical PK and PD sampling and PD testing need to be integrated at specific post-dose timings. Also, some of the PD tests require the inclusion of specific populations related to the targeted disease. As a consequence, operational execution of early phase trials has become even more challenging.

Although a “perfect” protocol may have been created on paper, many study aspects need to be evaluated from a practical point of view. These include:

- The recruitability of the exact study population

- Investigational Medicinal Product (IMP) preparation steps
- The use of sentinel dosing groups
- Sample-handling processes
- The frequency and types of assessments

Despite timeline pressures, clear communication on content and operational feasibility is key to avoid issues. During a feasibility review and subsequent trial preparation, all worst-case scenarios need to be considered – as the laws of Murphy and Hofstadter also apply to clinical research. With some complex assessment schedules, it is often best to organize a mock test run.



CASE STUDY 1

The importance of a thorough feasibility review.

SGS reviewed a multiple dosing study designed to assess safety, pharmacokinetics and age effect.

The draft protocol of this multiple dosing study contained three different age groups: 18-50y, 65-75y, and >75y. After careful review, the team defined following criteria as not feasible:

- Subjects among different age groups needed to be weight-matched
- Some of the normal ranges for vital signs and laboratory values were too strict for the oldest age group
- Concomitant medication taken by elderly subjects needed to be taken into account.

- The study required many ambulatory visits, creating extra burden for those in the oldest age group >75y

After an open discussion with the client, important compromises were implemented, without jeopardizing the scientific value of the data nor the recruitment and retention of the older population. In summary:

- The weight matching was phrased more flexibly allowing a slightly bigger deviation

- Normal ranges were changed, where possible, for safety and some concomitant medication were allowed
- Importantly, the revised protocol contained flexibility for the eldest group to choose between in-house stays or ambulatory visits



CASE STUDY 2

The importance of thorough risk assessment and study planning.

A US Biotech contacted SGS to perform a phase 1 study in healthy subjects with a seasonal allergy.

After a single ascending dose in healthy volunteers to assess safety and pharmacokinetics, the study included a second part to assess pharmacodynamic effects in healthy people with a seasonal allergy. The pharmacodynamic tests consisted in a nasal challenge to provoke rhinitis, a skin prick inducing a flare and a food challenge inducing oral allergy symptoms. After a nasal challenge, different read-outs for rhinitis severity were combined using a symptom score card, peak nasal inspiratory flow and nasal aspirate for inflammation analyses.

Careful review of the protocol identified some practical risks:

- As many allergic people have more than one allergy, the in- and exclusion criteria could not be too restrictive so as to exclude all co-allergies
- As people could not have rhinitis symptoms at baseline, the study needed to be conducted outside the allergy season, putting some time constraint on the study timelines
- People needed to respond to the nasal challenge to a certain extent to be able to measure an IMP effect, but putting the response criteria to severe would lead to a high screen failure rate
- The pharmacodynamic tests involved many assessments that were time critical, time consuming and needed to be performed in a standardized way

Following measures were taken:

- A workable solution was found to describe eligibility criteria, allowing those allergies that would not cause rhinitis, or could be avoided during the study
- To reduce the risk of not finishing the trial before the allergy season due to unforeseen set-backs (remember the two laws!) the trial was conducted at 2 sites, recruiting in a competitive way
- The criteria for challenge responses were evaluated together with a local specialist to predict the screen failure rate
- Staff were trained to perform the pharmacodynamic tests by a specialist and a dummy run provided real-life estimates of the timings

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