Good morning,

I am grateful to the organisers for the opportunity given to me to present you the very first results of the Optimon trial.
Optimon compared two monitoring strategies. One is based on industry practice, and was very intensive, with 100% data monitored onsite addressed. The other one was risk-adapted, depending on the risk encountered by the participant in the research study. This risk was assessed through a four-level risk scale, A being the lower level and D the higher.

Optimon assessed the hypothesis that it is possible to define a priori a risk-adapted monitoring strategy for each study, which will provide results similar to those of the 100% onsite strategy on the main study quality criteria, and will improve other aspects such as costs or delays of study completion.

This is a typical non inferiority situation.
So Optimon is a cluster randomised non inferiority trial. Academic Clinical Research Centres proposed studies and investigator sites, which included participants.

A Validation Committee has been set up to validate the risk encountered by the participant in the study, and the practical implementation in the study of the standardised monitoring plan defined in Optimon protocol.

There was no eligibility criteria for the participant. Studies with the higher risk level were excluded because for this type of study, intensive onsite monitoring is required. The CRC had to be experimented and GCP-compliant.
Randomisation applied to the investigator site and was stratified on risk level and study. The randomised strategy was either the 100% onsite or risk-adapted strategy.
For the 100% onsite strategy, all data of all participants in all sites had to be monitored onsite.

Conversely, for the risk-adapted strategy, intensity of onsite monitoring decreased with the risk level. There was one visit per site for risk level C, the highest within Optimon, but none at all for risk level A, the lowest.
Participants were included in the study, and their charts were monitored following the randomisation strategy.
After final cleaning, data were transferred to the Optimon team.
Optimon CRAs went then onsite to check the data accuracy.

Optimon main outcome was the proportion of participant charts without non-conformity on consent signature, SAE notification, the main eligibility criteria, and the study main outcome.

The Optimon Validation Committee outcome validated this composite outcome.

Secondary outcomes dealt with non-conformities, costs and delays.
Sample size had been calculated for a non inferiority margin of 11%, with the assumption of a 95% success rate in the 100% onsite strategy, and a high intra-site correlation of 60%.

So 900 participants were expected to be included.
More than 100 structures were contacted. Twenty-three proposed 59 studies, among which 22 were finally included.

There were 8 studies with risk level A, 4 with risk level B, and 10 with risk level C.

Twenty were biomedical researches, and 15 were trials.

All great clinical fields were present, but for cardio-vascular diseases.

Nineteen studies dealt with chronic diseases.

Ten studies were on specific populations: men, women, children, or elders.
From these 22 studies, we expected 83 sites and 954 participants, but some sites included only few of no participants. Finally, only 759 participants were included in 68 investigator sites.

Sex ratio was close to one.

The youngest participant was a few months old, and the oldest was 92. Disease duration ranged from 1 day to 48 years.
Before coming to the results, I would like to discuss what is called a non conformity within Optimon. It is a gap from protocol or GCP generated by the site, and not detected by the CRC, so remaining in the database after application of the randomised monitoring strategy.

Moreover, the Validation Committee distinguish the major non conformities as those particularly serious as regards to participant’s rights and safety and study results validity. Since this definition seems to lack specificity, I will give a few examples.

Consent form must be signed by a qualified physician, but we found forms signed by a resident.

Any SAE must be notified, but we found a sepsis that was not notified.

For a composite major eligibility criterion, one of the component was a waist size below a certain cutoff. So the physician had to measured it with a tape, and to report the measure in the participant’s chart for later check. We found out that one physician systematically assessed waist size visually and never reported it in the chart.

Finally, one of the sub-criteria of the main outcome of a study was the CD4+ lymphocytes count. We found a value of 1086 in the participant chart, while the database mentioned 730.

As you see, these errors are really serious and deal with key data.
One-thousand-and-two non conformities were detected by Optimon CRAs after application of the monitoring strategy, among which 465 were major non conformities. In the following I will comment results on major non conformities only. Half of major non conformities dealt with the main outcome, and the other half was equally split into the other categories.
The proportion of participant charts without non conformity was 63%.

This proportion raised to 66% for the 100% onsite strategy, and was only 60% in the risk-adapted strategy.

Altogether, more than a third of participant charts had at least one major non conformity after application of the randomised monitoring strategy.
I will not go into details concerning the statistical aspects of for the test of comparison of strategies, which is done through a model.

The difference between strategies within this model is 8%, which is rather small.

The upper one-sided confidence limit of the difference between strategies on the main outcome is 22%, far beyond the non inferiority margin fixed a priori to 11%. So the non inferiority of the risk-adapted strategy is not demonstrated.
Two explanations may be given to this failure to demonstrate non inferiority. First, though the difference between strategies is rather small and may be considered acceptable, it is too large compared to the non inferiority margin of 11%.

More importantly, the a posteriori power is small, for participants and sites accrual was far below what was expected.

Finally, the main result is that none of the strategies comes near the level of quality that is to be expected: less than a third of participant charts without major non conformity is really low, and far below the target of 95% used for trial sample size calculation.

Several explanations may be found. First, some CRCs systematically ignore a few errors, so that their performance rate is highly decreased. However, even the "good" CRCs do not reach the target, the best one being at 89% only.

Moreover, our initial assumption was certainly too optimistic. We thought that GCP were fully assimilated and implemented, at least for the key data, by the French academic clinical research, and this is not true. A large effort of improvement has still to be done.

Finally, maybe the Optimon CRAs have been over meticulous in searching for non conformities and they found too much. After all, the GCP guideline is no practical handbook, and the non conformity definition depends on its interpretation. The Validation Committee long-considered the question and advocates an implementation of GCP following its spirit, not the precautionary principle.
These results are disappointing in more than one way. Yet, Optimon allowed to collect unique data on the nature of non conformities observed in real life in various studies. These data will help us to identify areas for improvement.

Statistical analysis is far from being over, but there is obviously a problem with the writing of the consent form that leads to errors. The writing of the CRF for composite outcomes, either eligibility criteria or outcomes, gives rise to many non conformities. Finally, participant charts are too often incomplete.

So we must now be creative, and propose tools helping sites to do less errors, and CRCs to better detect them. For instance, the masked consent form proved efficient. Another interesting idea is statistical monitoring, which takes advantage of monitoring data collected in the database, specially for eCRF.

Finally, a debate should be started and quality objectives should be reconsidered. The zero defect target cannot be reached, and is probably useless. Major non conformities on key data should be targeted in priority. More than ever, GCP should be re-interpreted and its gaps should be pointed out.
To finish, I would like to thank sponsors and CRCs that included their studies in Optimon…
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Thank you for your attention.