N-SIDE

CASE STUDY

Clinical trial optimization at protocol design

MERCK

Context

When Merck was developing the clinical protocols for three oncological trials within a strategic clinical program, they reached out to N-SIDE. The main goal was to reduce waste and budget for these complex trials that required expensive comparators.

A clinical trial design which has not been optimized for supply chain aspects is a major driver of waste and cost. Clinical supply optimization can empower decision making during trial protocol design by allowing comparison of different scenarios. The impact of these crucial, early decisions is quantified and easily communicated across departments, allowing for improvements to the trial protocol.

N-SIDE clinical supply experts collaborated with the Clinical Supply team at Merck during the clinical trial design stage for three trials in an important oncological clinical program. All three trials had expensive comparators. Trials 2 & 3 in this program had identical design and are considered together in the case study.

N-SIDE clinical supply experts, with experience optimizing many different types of clinical trials, brought innovative approaches to reduce drug waste and save costs. The N-SIDE **Supply App** was used in order to optimize the trial protocols and provide factual support for decision-making.

With the results from N-SIDE, the Clinical Supply team at Merck was able take fact-based decisions. These trial design decisions were taken in collaboration with the Clinical team. Cross-department collaboration with the Clinical team was increased thanks to the clear impact analysis and quantified results. The project exceeded the targets for waste reduction and cost savings, all while ensuring patients were kept at the heart of the trial designs.

Solutions & results

N-SIDE clinical supply experts identified innovative opportunities to improve the trial design in terms of drug waste and cost impact. The main areas of improvement across the trial designs were:

The values and percentage of cost reduction are the result of comparing different scenarios with the initial strategy. This strategy is already optimized in terms of overage, costs and risk.

If we were to compare the different scenarios with a non-optimized strategy, the impact would be even greater and more impactful.

1 Kit design

The design of the kits for the trial is a decision that must be taken upfront and one that has a huge impact on the waste levels and costs of the trial. The impact of kit design is nearly impossible to assess using only a spreadsheet because of all the information that influences it. The optimal kit design for the trial cannot be identified in isolation of the full picture of the trial, including overall trial design, constraints and risk.

N-SIDE clinical supply experts using the **Supply App** were able to assess the kit design possibilities for the three trials, resulting in remarkable cost and waste reductions.

TRIAL #1

Comparator kit design optimization (1 vs 2 vials per kit)

CHALLENGES

What would be the best design to reduce the total waste of vials and sourcing costs?

SOLUTIONS

Option 1: 1 vial per kit
Option 2: 2 vials per kit

RESULTS

Packaging 1 vial per kit instead of 2 allows to **reduce the total material cost by 24%**

Total number of vials **reduced by 2529**

€24.4M of cost savings

Waste reduced by **41%**

TRIALS #2&3

IMP kit design optimization

CHALLENGES

- 3 options available.
- Select the best cost-efficient design.

SOLUTIONS

1

Formulation 1

Separate kits: active kit (10 days of treatment) + comparator kit

2

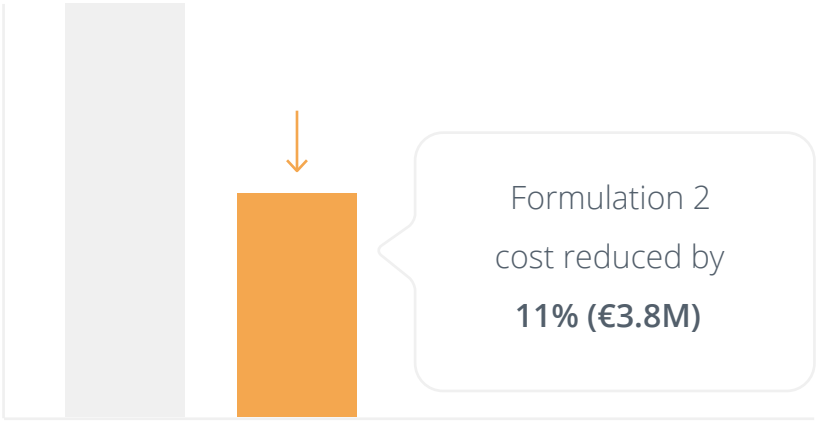
Formulation 2

Separate kits: active kit (30 days of treatment) + comparator kit

3

Combined kits: active (30 days of treatment) and comparator in the same kit

RESULTS



Formulation 2 was the best one in terms of costs; **total cost reduced by 11% (€3.8M)** compared to the other options.

2 Visit interval

Typically visit interval is not something that the Clinical Trial Supply team would challenge by default. Visit interval is defined in the protocol and not easy to assess the impact it has. With the N-SIDE solution, innovative ideas can be identified on how to optimize the visit interval considering all the trial specifications. Thus, drug waste and cost can be minimized without impacting the patient centricity of the trial.

In this case, optimizing the visit interval for trials 2 & 3 brought overall improvement to the trial design.

TRIALS #2&3

CHALLENGES

- 12 weeks of visit interval during all treatment;
- 6 kits dispensed per visit → high level of stock needed at site for the randomization visit;
- High level of buffers to cover the randomization visit (with a recruitment period of 24 months → high level of waste).

SOLUTIONS

N-SIDE proposed solutions: test the optimal visit interval → find the best balance between material cost, clinical visits cost, shipping cost (and patient centricity)

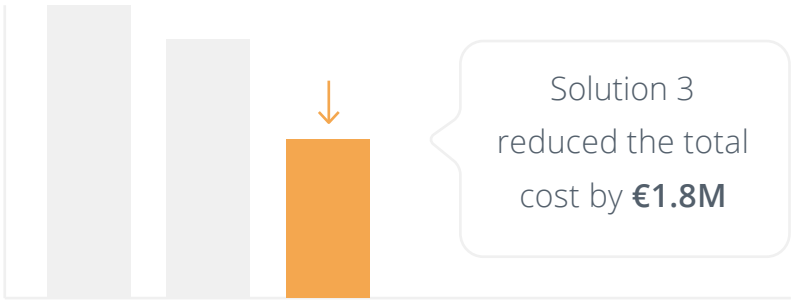
1. Reduce the visit interval from 12 to 4 weeks for the entire treatment.
2. Reduce the visit interval from 12 to 8 weeks for the entire treatment.
3. Add one visit to reduce only the first visit interval from 12 to 4+8 weeks (12 weeks interval for the rest of the treatment).

RESULTS

Solution 1 & 2 (4 and 8 weeks): significant reduction in waste and cost, but strategy not feasible due to the high increase in the number of clinical visits. Costs, site and patient centricity were all considered.

Solution 3: 4+8+12 weeks interval (changing only the first visit interval).

- Total cost: reduced by **€1.8M**;
- Overage: reduced from **32% to 23%**;
- #clinical visits: increased only by **13%**



Solution 3 was selected and implemented. Reducing only the interval of the 1st visit from 12 to 4+8 weeks (12 weeks for the rest of the treatment) **reduced the total cost by €1.8M** without greatly increasing the total number of visits. Additionally, the waste at site-level was greatly reduced with this approach.

Very important collaboration and communication between CTS and Clinical team took place to arrive at this optimal design. The clinical team validated that this solution was feasible without adversely impacting patients.

Having the facts about the visit window impact allowed for clear assessment and early collaboration between the CTS and Clinical Team. Considering both the patient centricity and the supply impacts together led to identifying the best design.

3 IRT optimization and trial design

Given the particular design of this trial, N-SIDE clinical supply experts identified a way to further reduce drug waste by avoiding static buffers on the comparator treatment arm.

This particular clinical trial had an open-label comparator treatment arm and very high comparator sourcing costs. N-SIDE experts identified the opportunity to optimize the trial design and IRT settings together in order to avoid static buffers for the comparator.

TRIAL #1

CHALLENGES

Comparator waste reduction at site-level.

- 90% of comparator drug waste was at site-level due to a complex supply network, short shelf life, and a long recruitment period with several expiry replacements.
- The comparator was also very expensive to source.

SOLUTIONS

First solution: Guarantee a minimum screening that is longer than the site shipping lead time. This eliminates the need for buffers on site to cover the first dispensing visit. With these conditions, a “smart prediction” IRT strategy can be implemented.

If we have a screening period that is shorter than the shipping time, buffers need to be sent to sites to cover the first visit.

The disadvantages before this solution were:

- All sites must be stocked with buffers even if there are no patients in screening. With a short shelf-life there will be frequent replacement, even if there are no patients at those sites.
- To have a safe strategy, the buffer levels must be high enough to cover worst case scenarios.

The solution increases the screening period and guarantees that the kits can arrive at site before the randomization. Patient needs are predicted in a smart way and kits will be only sent if there are patients and if there are no kits in stock at site.

The advantages to this solution are:

- Buffers are not needed and, as a consequence, expiry replacements are avoided.
- This is a very safe strategy that is based on the actual number of patients in screening.

This was discussed and validated with the clinical team to guarantee a minimum screening period without impact for patients.

This was indeed a very positive solution, but still not enough. Comparator kits were sent to sites to cover the possibility of randomization on that treatment arm. Considering that the trial has multiple treatment arms and a short shelf-life, the chances that comparator kits would expire unused at site were still high.

Second solution: Implement pre-randomization for the comparator treatment arm. This way comparator kits are only sent to sites if patients are pre-randomized on that treatment arm.

After screening, patients are assigned to a treatment arm without receiving any kit. If, and only if, those patients are pre-randomized on the comparator treatment arm, these kits will be shipped to sites. Otherwise, the stock remains at depot level.

This will reduce the waste linked to the uncertainty of the randomization and increase the dispensation rate.

RESULTS

Solutions 1 & 2

Pre-randomization of the comparator kit combined with smart prediction allows us to **reduce the total sourcing cost by 23% (€18M of cost savings)**, while ensuring 100% patient service level.

The expected drug waste at site level was **reduced by more than 40%.**

Comparator waste **reduced by 38%.**

Optimizing the IRT settings alone would not have achieved the same results as an integrated approach of considering the IRT settings and the trial design early on and taking a global view.

4 Accelerate time-to-market by reducing the recruitment period

In order to speed up the timelines, it is critical to assess if there will be any bottlenecks coming from the supply chain. N-SIDE experts tested the impact of accelerating the recruitment period for trials 2 and 3 and examined the requirements of the clinical supply chain.

With the facts from the optimization results, the Merck Clinical Trial Supply team was able to take a decision to reduce the recruitment period for the two trials, confident that supply would not be a bottleneck and that costs were managed.

TRIAL #2&3

CHALLENGE

Reduce the recruitment period to accelerate the time to market.

SOLUTIONS

Assess the impact of activating additional sites, countries and depots in order to speed up the recruitment period by 10 months.

RESULTS

By considerably increasing the number of countries/sites/depots, recruitment can be reduced by 10 months. DP/IMP **production increased by only 12%.**

N-SIDE results showed that **DP/IMP production will NOT be the bottleneck** in case the number of countries/sites/depots doubles to speed up recruitment.

Merck took this decision and **achieved the 10 month acceleration** across the 2 trials.

The Clinical Trial Supply team at Merck was not the bottleneck for accelerating this recruitment, in fact all bottlenecks were avoided and the ambition achieved. The overall R&D program was accelerated thanks to this initiative.

Conclusion

Optimizing early, during clinical trial design, presents an important opportunity to reduce drug waste and cost, as well as accelerate timelines. Every aspect of a clinical trial design needs to be considered and can be optimized.

In this case study, the kit design, visit intervals, IRT settings with overall trial design, and recruitment were the opportunities that yielded the most important results. Depending on the specificities of the trial, there are other areas that can also be optimized, such as country selection/feasibility, titration scheme, direct-to-patient, stratification, etc. N-SIDE brings innovative solutions to the table that are tailored to the individual characteristics of the trials.

Factual support to the early decision making can help the sponsor company take informed decisions and achieve a more supply-friendly clinical protocol. At the same time, cross-departmental collaboration is promoted with clear impact assessments of the decisions. Overall, waste, costs and timelines can be decreased while keeping a safe and robust trial design.

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Learn how N-SIDE's software and professional services can help life sciences companies optimize clinical trial design.

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