



IDDI CASE STUDIES

The following case studies demonstrate how the methodology and technology of IDDI were key in the conduct of the clinical trials.

Monitoring toxicities of a combination treatment in phase I

A new anti-cancer drug was going to undergo phase I testing to confirm its safety when added to a standard cytotoxic regimen. The trial would have to be stopped after accrual of a few patients in order to review toxicity data, and then re-opened if appropriate. IDDI proposed using innovative **technology** (web-based capture of only key toxicity data and immediate reporting of toxic events) to provide continuous assessment of the combination toxicity profile using pre-defined stopping rules.

Using minimization for a complex trial design

A multi-center phase II trial was conducted in just over 100 patients to compare metabolic changes in the prostate after administration of two treatments for locally advanced prostate cancer. The changes of interest were assessed by a biopsy taken at different randomized times and by magnetic resonance spectroscopy/magnetic resonance imaging (MRS/MRI) in about one third of randomly selected patients. In order to protect against chance imbalances, patients were additionally stratified by their level of prostate-specific antigen (PSA) at baseline. The **methodology** adopted to implement this complex trial design was minimization for the various randomized factors.

Bridging patient enrolment and remote data entry

A customized registration and randomization application using ID-net, IDDI portal dedicated to patient enrolment, was implemented for a phase II study in non-small cell lung cancer. IDDI implemented an automated data interchange process between ID-net and the Remote Data Entry (RDE) system using XML standard and Internet **technology**. Patient registration performed in ID-net populated a new patient record in the RDE system with consistent demographic data. Patient randomization using ID-net populated the stratification information and activated the adequate treatment form in the RDE system. This real time process increased the compliance of key patient data across systems and enhanced the effective use of RDE by the site personnel.

Analysing a biomarker as a proof of concept

Two doses of a therapeutic vaccine were tested simultaneously in a randomized phase II trial. While the trial's primary endpoint was not sensitive enough to show efficacy of either dose or any difference between the two, using the advanced statistical **methodology** of mixed modelling on repeated measures, it was found that the high dose had a highly significant effect on a relevant biomarker, while the low dose had no such effect. This proof of concept allowed the sponsor to raise additional funding to support further trials.



Jumping ahead to Phase III

A new ophthalmic drug was going to enter a phase II dose-ranging trial in order to determine the dose to use in phase III trials. IDDI proposed to jump ahead and test a dose-effect hypothesis in two pivotal phase III trials, using appropriate statistical **methodology** to adjust for multiple testing (simulations showed a step-up procedure to be slightly preferable to a closed-test procedure). Although the two trials were far larger than if a single dose had been used, this bold approach resulted in a gain of at least one year of clinical development. The drug has received approval by the FDA (Food and Drug Administration).

Using remote data entry for complex patient eligibility assessment

A randomised phase II trial was conducted to compare three chemotherapy regimens as First Line Therapy in Women with HER2 Negative Locally Recurrent or Metastasis Breast Cancer. Patient registration forms were designed by IDDI on its EDC platform and used by the sponsor to capture and check patient eligibility data. A dedicated interface between the EDC and the randomization (ID-net) was implemented: patient registration performed by the investigator in ID-net populated the patient registration forms in the EDC. The randomization step was enabled in ID-net when patient eligibility data was fully captured in the EDC platform. This integrated **technology** solution met sponsor's expectation in the patient screening process.

Validating adverse events on a large scale

Two pivotal trials were conducted (one in the US, one in Europe) to seek approval of a new treatment for a chronic condition in elderly patients. The safety of the new drug was of particular concern. Adverse events and medications were coded by IDDI using proprietary coding system ID-code, based on the standard MedDRA and WHO-drug dictionaries. More importantly, the large volume of over 36,000 coded terms could easily be validated by the Sponsor using real-time, web-based **technology**. This cut the time required by several months, and the budget by almost half a million dollars.

Validation of a genetic signature for women with node-negative breast cancer

A 70-gene signature was shown in a single institution to have prognostic value in patients with node-negative breast cancer. The purpose of this study was to validate this signature in independent patient samples. Hazard ratios were estimated by IDDI's **methodology** group of experts, to compare rates in high versus low risk groups for the time related endpoints. The models were or not stratified by a clinic-pathological risk group to verify if the gene signature adds independent prognostic information to clinic-pathological risk factor.

Applying likelihood method for data safety monitoring

Formal safety monitoring, often performed by independent committees of physicians, biostatisticians and ethicists, has become common in modern clinical trials. Safety monitoring often includes reading of many pages of tabulated adverse events classified by body system, type and severity. Monitors look for within treatment incidence and between treatment differences in incidence that may be of concern. Frequentist statistical **methodology** is not appropriate for this

type of surveillance due to multiplicity issues and the inappropriateness of the background repeated sampling assumption.

A safety monitoring committee in an international ophthalmology clinical trial used the principle of support and support intervals based on the log likelihood function for incidence parameter conditional on the data at hand. Rates were calculated as poisson random variables and support methods were used for both incidence and treatment differences.

Meta-analysis to assess efficacy in colorectal cancer

Tumor responses and survival were analyzed combining the data from the different trials using patient individual data. The statistical **methodology** was based on the classical notion of stratification, consisting of estimating a treatment effect within each trial, and then overall. A statistic for heterogeneity between the trials was calculated. A test of overall treatment effect was calculated. The following quantities were used in the calculation: O , which is the number of untoward events observed in the treatment group, E , which is the number of events that would be expected in the treatment group if there were no differences between treatment and control; and V , the variance of the number of events. Those data were shown graphically in a forest plot.

Detection of data exceptions in randomized trials using SMART

SMART (Statistical Monitoring Applied to Randomized Trials) is an original software developed at IDDI over the last three years. The software uses a rich catalogue of statistical tests that can be performed automatically on data from randomized multicenter trials. A large number of tests are carried out to compare each center to all others, so as to detect, with extremely high sensitivity, unusual patterns in the data. The tests include standard tests (e.g. for the comparison of means or variances) but also original tests (e.g. for the detection of digit preferences or calendar anomalies). Metrics are used to assess the plausibility of the data in all centers.

Discovering new prognostic biomarkers for breast cancer

A range of biological markers were analyzed by polymerase chain reaction and immunohistochemistry in tissue microarrays from patients treated in several past and ongoing clinical trials for breast cancer. The obtained marker measurements were combined with the clinical data and analyzed using survival analysis methodology, including some advanced modeling techniques, to investigate whether any of the markers had prognostic value. The investigation was successful for at least one of the potential markers analyzed. The project is ongoing to validate further biologically interesting candidate biomarkers.

A flexible phase I trial with randomization to placebo

The maximum tolerated dose of a new drug, supposed to alleviate some adverse effects of anti-cancer chemotherapy, was to be established in a phase I trial. To assess the safety of the drug, information on the background toxicity rate in the enrolled sample had to be collected. By using state-of-the-art methodology, a flexible design was proposed for the trial. It combined the use of the continual reassessment method on a continuous dose scale with a concurrent randomization to placebo. The properties of the design were investigated by conducting a simulation study, which allowed to fine-tune the final form of the trial design.