

The Population Pool

In the industry today, every wasted second can potentially incur losses for the sponsor. However, patient databases are on hand to define the optimal subject population, thereby reducing the risk of such delays by allowing the testing of criteria in advance of recruitment.



Medical informatic staff at work

Image: Ronen Topelberg

Joseph Azuri at Maccabi Healthcare Services

Efficient patient recruitment is one of the greatest challenges to sponsors of clinical trials. Too often, inclusion-exclusion criteria are specified, and only after months of unsuccessful recruitment efforts are the criteria redefined to yield an appropriate subject population – a process that can cost many months in valuable research time. A related challenge is no less daunting: once criteria are defined and refined, it can take a long time to identify the relevant sites and patients, and to mobilise them into the study.

In a recent article, Quintiles Senior VP, Christopher Cabell, wrote: “Imagine a world of readily available health data in which eligible trial participants could be identified and automatically alerted to clinical trials that could benefit them” (1). This world is becoming an everyday reality.

In executing trials using a clinical patient database, preliminary research can reduce the risk of non-feasible design and criteria before recruitment even begins. The database can be used to determine the availability of subjects as well as to identify sites with a critical mass of subjects per site. Iterations enable the development of optimal study design. Furthermore, once the design has been finalised, the database helps streamline the recruitment process by alerting physicians to the presence of eligible subjects. Such advanced medical informatics and expert clinical knowledge, combined with a vast database, yield outstanding results in protocol design and site/patient recruitment.

The Database and Registries

Maccabi Healthcare Services, Israel's second largest health fund, provides comprehensive medical coverage to nearly two million members. The patient database is derived from a central electronic medical record, containing longitudinal data on its stable population for over 18 years. All doctors have been computerised and connected to the central database since 1993, using a common and integrated IT system. A central medical record gives control over the quality and consistency of the data. The data is kept in a way that protects the privacy of patients and complies with confidentiality requirements.

The database compiles information on a real-time basis from various sources, including physicians, hospitals, pharmacies, a central laboratory, imaging centres, physiotherapy clinics, nursing stations, and psychiatry and mental health services. The database has been applied to create a number of disease registries (see Table 1).

The registries are built on the basis of computerised coded information, covering demographics, co-morbidities, laboratory results, medications, treatments, imaging and medical encounters (physicians, ancillary services, and hospitalisations). All data are collected daily through central synchronised tables, with automated quality assurance processes applied to the automatic data collection. Inclusion criteria are based on international guidelines if they exist, or are the result of a long process of validation. Validating the specificity and sensitivity of the information using different sets of criteria for the registries allows for constant database improvement processes.

Table 1: Maccabi's disease registries	
Registry	Number of patients (2011)
Diabetes	95,875
Cardiovascular diseases	82,153
Infertility	10,737
Obesity	244,125
Hypertension	257,727
Schizophrenia/bipolar	14,300
Cancer	45,430
Warfarin treatment	11,000
Chronic kidney disease	47,456
COPD	24,000
Home care	6,000

Source: Maccabi Healthcare Services

All patients have a single national identity number which enables contact with other national databases and sources of information. Some registries also include outsource information (for example, National Cancer Registry data).

Direct communication with primary physicians for case ascertainment and follow-up assures a high level of validity of the registries. Maccabi's clinical database was developed and is maintained and validated by a professional staff of physicians, epidemiologists, pharmacist and biostatisticians.

Defining and Identifying Appropriate Study Populations and Sites

A study's clinical protocol defines the precise inclusion and exclusion criteria for the study population. Given the criteria for a particular study, the Maccabi medical registries and database can identify the potential investigators, sites and study populations, targeting potential investigators with the largest population of patients best suited for the study. As described in the example below, this process enables early identification of studies for which the potential study population is too dispersed, rendering recruitment difficult and expensive. The study can then be redesigned using alternative recruitment strategies or modifications in the inclusion-exclusion criteria.

In contrast to the traditional approach to a new study, where potential investigators are asked to estimate the number of suitable subjects in their patient panels, Maccabi applies a two-step site selection process. Firstly, after receiving the study protocol the database is used to identify the potential investigators with the largest number of potential study subjects. At this point the impact of modifications of the inclusion-exclusion criteria on recruitment efficiency can be explored. In a recent study, out of approximately 90,000 diabetic patients, given the initial criteria, 500 eligible patients were identified who would have been dispersed among more than 200 physicians on a wide geographic area. This was considered infeasible. Careful redefinition of the criteria led to a doubling of the eligible

population, increasing the number of eligible patients per site and enabling the use of fewer sites. This redefinition was done with the guidance of a team of clinical experts who ascertained that the modification of criteria would not adversely affect the integrity of the study design. This cooperation between database and clinical experts often leads to more appropriate inclusion-exclusion criteria than initially defined by the sponsor. Naturally, the proposed changes are discussed and worked out with the sponsor to yield an optimal design.

Among the potential investigators identified in the first step, the most experienced in clinical studies in the particular field were also identified. A search for an investigator for a diabetes study seeking to recruit mild diabetics may finally lead us to a primary physician or a group practice, which might not have been the obvious investigators in the first place.

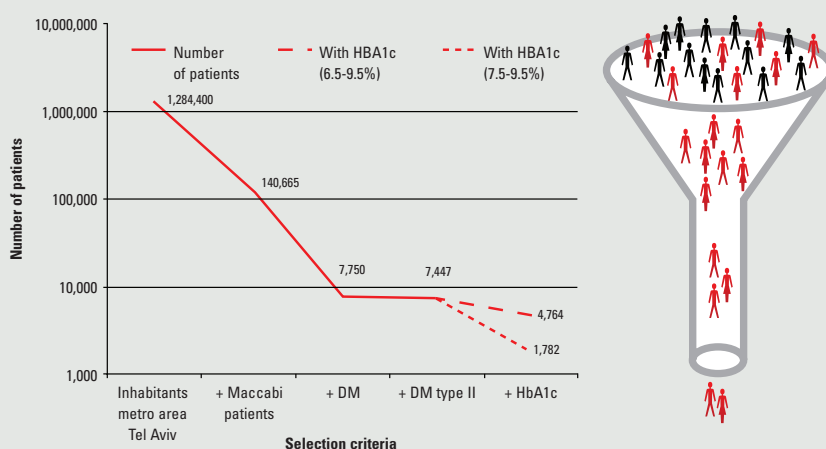
Real-Time Interaction with Physicians Shortens Recruitment Time

After identifying the optimal set of potential sites, the database and IT systems can also help in the recruitment process itself. The investigators receive an automatically generated list of their patients who may benefit from participating in the study. This enables the investigator to make direct contact with his or her patients. Moreover, as the investigator regularly uses a computer for routine clinic visits to update electronic medical records, any 'random' interaction with a patient who may benefit from participating in the study triggers a real-time alert to assist in his or her recruitment.

The case study below shows how these capabilities can be applied in ways that help to identify the appropriate target study populations and sites, streamlining the patient recruitment process.

In a Phase 3 study for a new oral contraceptive, the sponsor defined a study protocol that called for females of ages 18 to 40. The principal exclusion criteria were if the females: were

Figure 1: Impact of in- and exclusion criteria in clinical trials on the selection of eligible patients. The graph illustrates the change in numbers of eligible patients by varying selection criteria. The extension of the HbA1c range increases the number of available patients by a factor of 2.7



Source: Maccabi Healthcare Services

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Registry Data & Examples

Patient data consist of demographic information, co-morbidities, lab results, medications, treatments, imaging, medical documentation by physicians, paramedical providers, hospitals ...

Documented Patient Cases including:

- Diabetes 95,000
- Cardiovascular 82,100
- Obesity 244,100
- Hypertension 259,000
- Cancer 45,500
- Schizophrenia/Bipolar 15,000
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For further information please contact:

David Surjo, Ph.D. / VP Business Development
Telephone: +49 26 32 - 99 27 84
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Image: Anne Dubitzky

undergoing menopause; were pregnant; were six months post-birth or abortion; had pathological BMI; were a smoker over the age of 34; were diabetic; were suffering from chronic renal disease; had cancer; had uncontrolled/untreated hypertension; had abnormal pap smear; were hepatitis C positive; had obstructive jaundice; or had abnormal liver function.

Applying this criteria, the database initially identified more than 20,000 potential subjects over a fairly expansive geographic area, at multiple sites. The number of sites was then narrowed down to be in line with the preferred geographic area for the study. In a final step, the particular sites chosen were the preferred group of physicians (based on their previous experience with relevant trials), resulting in including 1,200 potential subjects at five potential sites.

The study manager defined rules to automatically activate the alert engine whenever a potential study subject (identified above) met one of the identified physicians. The alert automatically pops up when the potential subject swipes her health plan membership card. At this point, the physician may ask the subject questions (or examine her), in order to ascertain if she matched the study requirements. This covered issues not included in the database or potentially not up-to-date in the records, or verification of particular items, as required. Exemplary questions included: known history of previously unreported significant adverse events during oral contraceptive use; use of IUD at the time of the visit; drug or alcohol addiction during the preceding year; participation in other clinical studies; and HIV.

This final step included filling out a structured questionnaire that enabled finalising the subject pool identification process. In the very near future, the questionnaire will pop-up automatically on the physician's computer right after the alert. The physician will be able to fill out the questionnaire on the computer in real-time and submit to the study manager. This will also save effort



and time on the part of the physician, while automating and rationalising the process.

Conclusion

Clinical patient databases enable researchers to model their studies in advance on real population data. Using these data, the various clinical design models can be pre-tested on actual populations, eliminating the trial and error of research design, shortening the overall time required, and reducing risk often involved in clinical trials. Furthermore, online and real-time identification of subjects and alerts to physicians can substantially streamline and shorten the recruitment process. The bottom line of this approach is shorter studies, lower risk and enhanced cost-effectiveness in clinical trials.

Reference

1. Cabell C, Data-driven patient recruitment to deliver qualified patients, faster, Quintiles white paper, March 2010, www.quintiles.com/information-library/white-papers

About the author



Joseph Azuri has a degree in Medicine from the Hebrew University and Hadassah Faculty of Jerusalem, and is a faculty member in the Tel Aviv University faculty of medicine. He is a family practitioner, and holds an active clinic near Tel Aviv. He has been the head of the unit of Clinical Studies in Maccabi Healthcare

Services for the past nine years and a member in two IRB committees in Israel. Each year his unit conducts nearly 150 clinical trials in the community in various fields of medicine. In recent years he took an active part in the legislation process of clinical trials in Israel. Email: azuri_yo@mac.org.il

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For further information please contact:

David Surjo, Ph.D. / VP Business Development
 Telephone: +49 26 32 - 99 27 84
 E-Mail: david.surjo@crs-group.de
 Web: www.crs-group.de

