www.hcltech.com

LIFE SCIENCES & HEALTHCARE
A lifetime of care

Patient Recruitment and Retention Strategy in Clinical Trials: Data-driven and Evidence-based Approach

Narender Dureja, Nidhi Bajpai

WHITEPAPER

DECEMBER 2014

TABLE OF CONTENTS

PROBLEM STATEMENT

In a clinical trial considering different phases, there is a need for subjects to be enrolled as per the eligibility criteria defined in the study protocol. Aiming and holding the involvement of the suitable patients places a critical challenge for investigators and sponsors of the trial. During the conduct-phase of clinical trials, sites usually spend most of their time on patient recruitment, and yet, statistics show that despite their efforts, reaching enrollment goals per timelines seem elusive in many studies.[1] The majority (nearly 86%) of clinical trials conducted in the United States fail to enroll subjects within the contract period.[2] It is commonly observed that once the desired subject count is achieved for a study, activities required to enhance patient retention gets ignored. This may result in nearly one-quarter of study volunteers drop out before completing the study. [3]

The industry perspective reflects that it is the unabridged responsibility of the investigator to recruit and retain patients in clinical trials. Thus sponsors totally depend on healthcare professionals, who in turn, leave it to patient's foot fall to the site to achieve study enrollment objectives. Typically the methodology adopted is generic in nature[3] i.e. the same technique for subject recruitment is embraced for trials of different therapeutic areas. Also, the same groups of patients are referred from the site's internal database for different trials. Literature suggests that the bulk of prescreened eligible subjects are lost before they are enrolled.

Too small a subject pool or localized sites in a particular geography can incorporate an element of bias in the study. The challenge is underlined by heavy competition among players in the same therapeutic area. Poor enrollment and retention warrants for extra cost, as replacement patients and rescue sites may mean more overheads, wastage of study resources, increased timelines, lesser accuracy, protocol deviations and decreased return on investment (ROI).

In today's competitive market, "hoping" for success is not a visible option,[4] it is about adding scientific maneuvers underlined by sophisticated technological advancements to meet global upsurge of subject enrollment and retention loads in clinical trials.

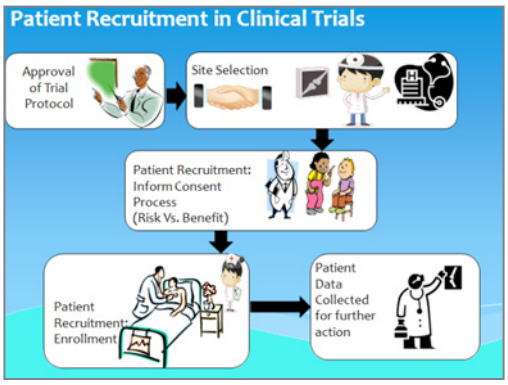
WHAT IS THE CURRENT PROCESS?

E6-GCP guidelines suggest that an investigator should have adequate resources to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.[5]

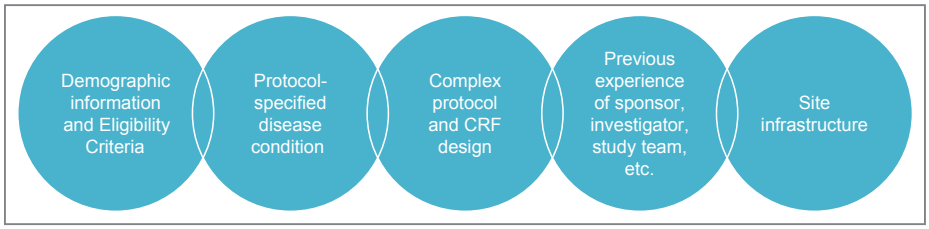
There are many different recruitment methods, including media (i.e., television, radio and newspaper), physician referrals, press releases, fliers, random mailings, cold calls and the internet.[6]

These methods must be selected before study start. Also, some common factors such as-sample size, suitability of the strategy as per study design and overall budgetary constraints must not be ignored.

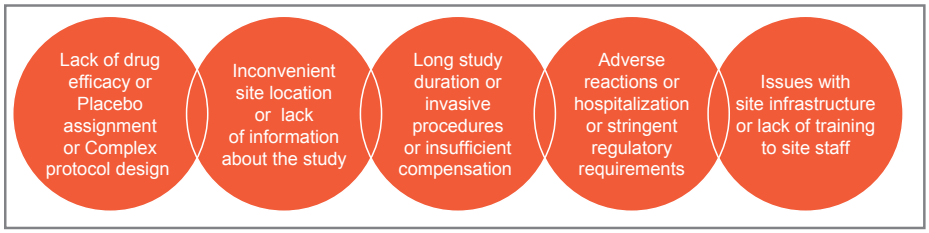
The below diagram depicts the process of patient recruitment in clinical trials.



Some of the common factors which may influence patient recruitment and enrollment are:



Some of the common factors which may influence motivation[3] level of subject(s) to continue in the study are:



Existing approaches to recruitment for clinical trials do not pinpoint a satisfactory number of subjects in a time- and cost-effective fashion. These methods fail to match the scalability with respect to the rising requirements of the industry.

PROPOSED APPROACH: HCL'S POINT OF VIEW (POV)

We support data-driven and evidence-based approach wherein the ROI increases as the level of competency at the site is made to extend from 'local random strategies' to the combination of 'centralized approach and/or real-time metrics'.[4] This will help optimize recruitment and retention efforts through methods which are more of predictive than speculative. This falls in line with the old management adage "You can't manage what you don't measure"![7]

This will be done by deriving real-time or near real-time matrix through set of databases covering multiple clinical trial registries, enterprise data, claims/hospital discharge data, etc.

Once the target for recruitment is achieved, diligent patient tracking will be done through call centers.

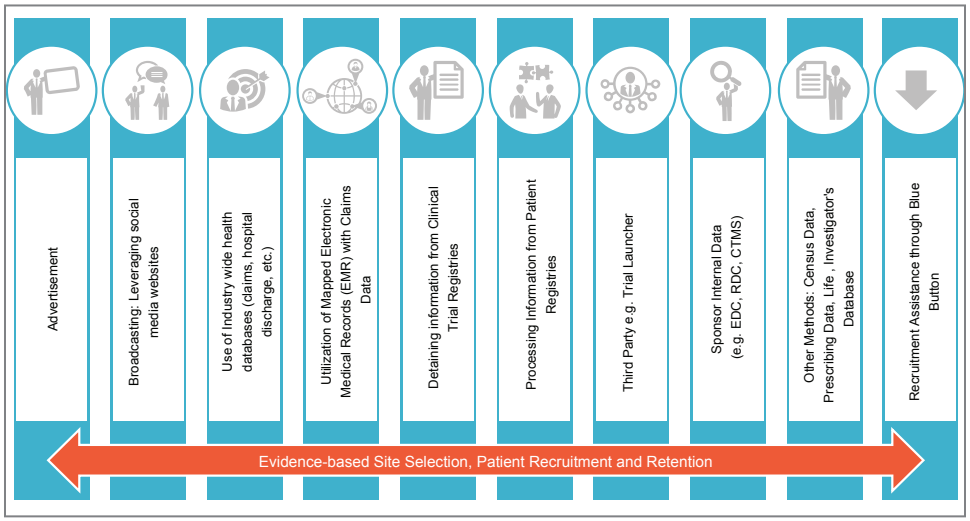
Following are highlights of HCL's Patient Support Program[8]

- 24/7 access to valuable online tools and resources
- Access to registered nurses, clinicians and pharmacists
- Site training material for patients, customized to geographical and regulatory compliances
- Exhaustive monitoring—with focus on protocol requirements—to better identify risk, non-compliance and poor performance and timely reporting of adverse events
- Planning for patient-visit schedules according to study parameters
- Reminder support alerts for missed appointments and medication
- Analysis of data trends including enrollment/dropout status and adverse events
- Fitness, diet counseling, smoking cessation and alcohol reduction programs
- Caregiver support as per criticality/complexity of disease in the trial

PROPOSED SOLUTIONS FOR SUBJECT RECRUITMENT

To ensure progressive, on-time patient recruitment in a trial, a combination of the following methods can be adopted:

GCP recommends that before initiating a trial, the investigator/institution should have an approval from the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) for the subject recruitment procedures (such as advertisements) along with any other written information that needs to be provided to the subjects.[5]

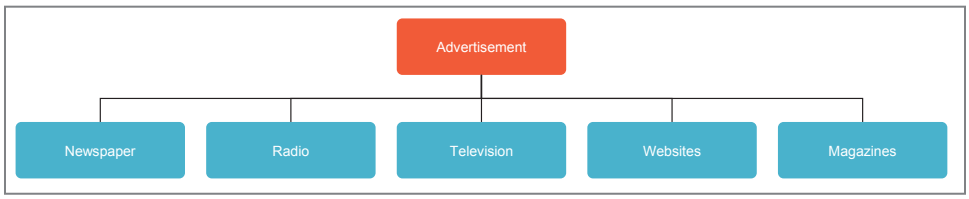


SOLUTION DETAILS

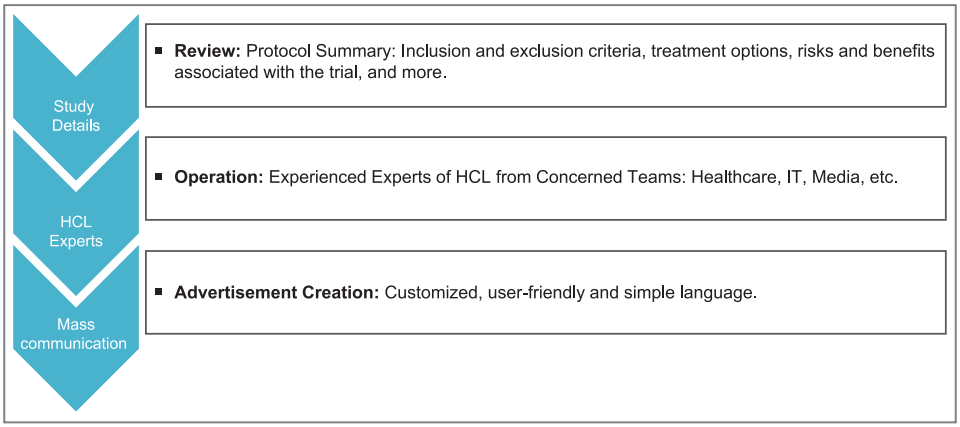
HCL has developed a strategy to address patient recruitment requirements for a clinical trial. A brief description of the process flow of our modeling is given below:

1. Advertisement

Channels of mass communication such as newspapers, radio, television and websites can be leveraged to advertise for subject recruitment.

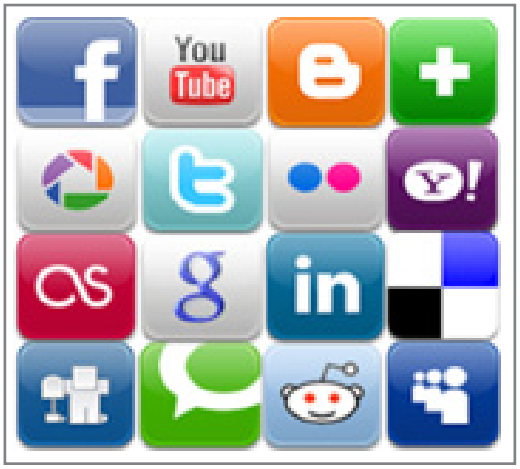


Customized user-friendly websites will be developed by our experienced experts to make patients aware about details of the clinical research study for the site. The process flow adopted may include steps outlined below:

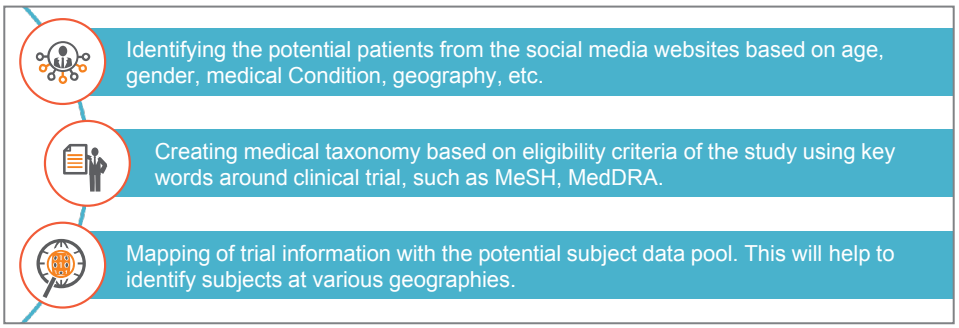


2. Broadcasting: Leveraging Social Media Websites

The use of social networking channels such as Facebook, Twitter, MySpace, YouTube, and patient websites could help reach out to the relevant subjects. This method can be useful in collecting near real-time information as and when it's updated by the patient.



Method can be deployed as follows:



Following is an example of Tag Cloud created for the Type 2 Diabetes for trial key words:

Reference: Internal evaluation of Social Network Data

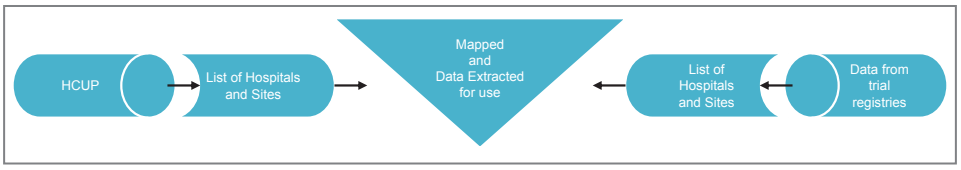
Sentiment analysis about doctors can be derived with the help of the ratings done by patients on web sites such as Vitals, Ratemds, Healthgrades, Zocdoc, etc.

3. Use of Industrywide health databases (claims, hospital discharge, etc.)

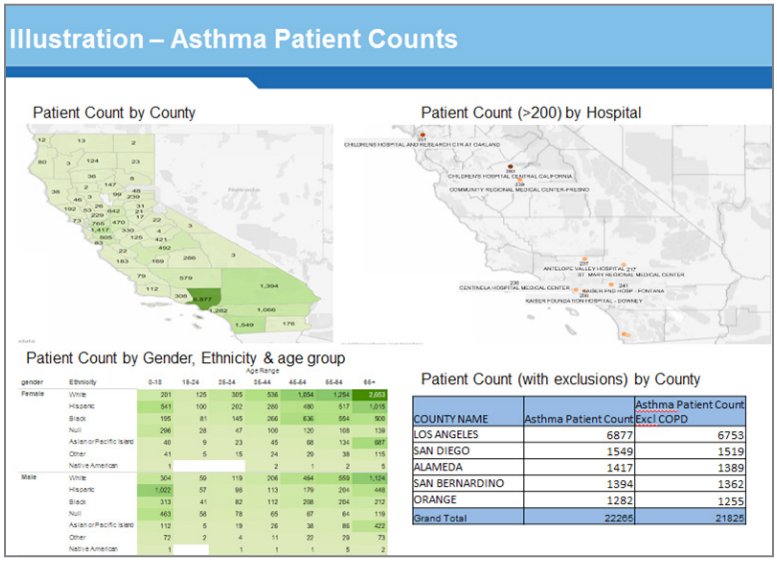
Healthcare Cost and Utilization Project (HCUP) databases contain information on in-patient stays, emergency department visits, and ambulatory care.[9]

HCUP databases can be used for patient recruitment as outlined below:

- The list of hospitals that have treated a specific set of patients will be derived.
- Thus, the information about doctors and the site can be extracted for a particular therapeutic area.
- This will be mapped with the trial information i.e. key words derived from study eligibility criteria.
- Using trial registries, the information will be further analyzed and extrapolated to derive the past and present experiences of the investigator and site in clinical research in terms of patient enrollment, trial completion status, etc.



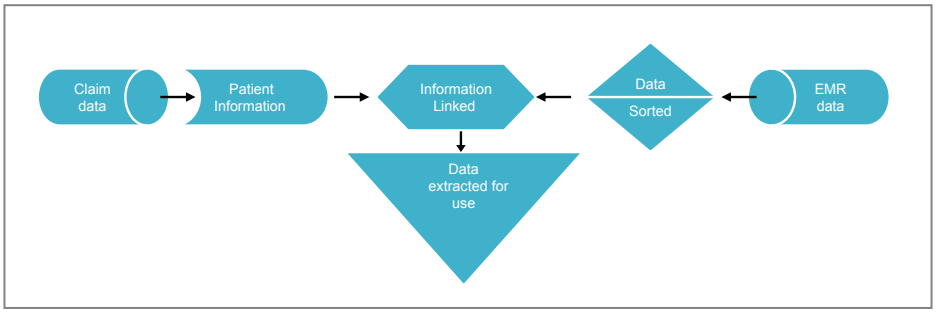
Following image depicts the geographical clusters of 'Asthmatic Patients Count' by—country, hospital, gender, ethnicity and age group:



Reference: Internal Evaluation of HCUP Data

4. Utilization of Mapped Electronic Medical Records (EMR) with Claims Data

- Claims include information related to medical services (in-patient, out-patient, pharmacy, etc.) provided to patients. The information is not in detail and has high level of ICD coding, with missing severity about the condition.
- EMR data has exhaustive laboratory results, vitals, clinical data, etc., collected at the point of care.
- Above two can be used to the sponsor's advantage for enhancing subject recruitment by linking claim data with EMR and thus enabling to critically evaluate patient's eligibility for the trial.
- Based on this, these patients and sites may be contacted for enrollment in the study and thus the process could accelerate the rate of patient recruitment.

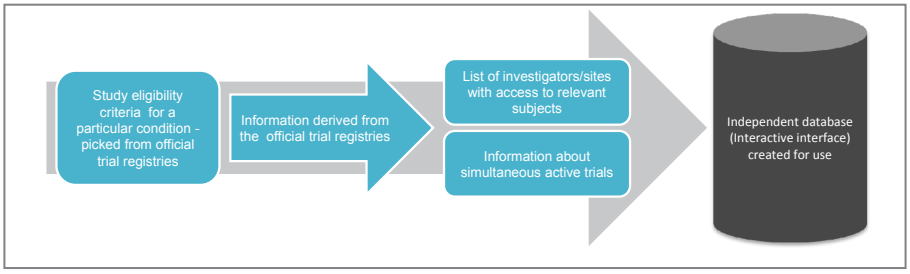


5. Detaining Information from Clinical Trial Registries

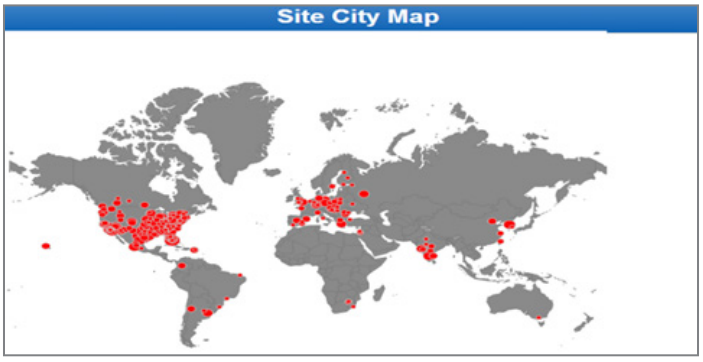
On the basis of the data available on various clinical trial registries, including but not limited to- clinicaltrials.gov/, www.clinicaltrialsregister.eu/ and apps.who.int/trialsearch/, an interactive interface will be created. The information derived will be mapped with the trial key words to help pick the sites with the best historical performance around the world. Thus the right sites can be reached with the naïve patient populations for the studies.

The process adopted will be executed as follows:

- The inclusion/exclusion criteria for studies with required status will be picked from the official registries to derive the list of investigators/sites for a particular therapeutic area.
- This will substantiate the fact that these investigators/sites have access to relevant subjects.



Following is an example of a site map of different cities where the trial on Type 2 Diabetes was conducted. This map is based on the information provided in FDA's clinical trial registry.



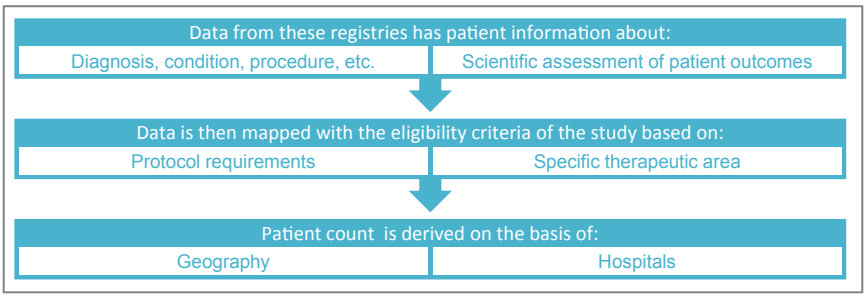
Reference: Internal evaluation of Clinical Trial Registry Data

6. Processing Information from Patient Registries

Disease or patient registries are collections of secondary data related to patients with a specific diagnosis, condition or procedure etc.[10] A patient registry is thus an organized system that uses observational research methods to collect data for the scientific assessment of patient outcomes.[11]

- Disease or patient registries are collections of secondary data related to patients with a specific diagnosis, condition or procedure etc.

- A patient registry is thus an organized system that uses observational research methods to collect data for the scientific assessment of patient outcomes.

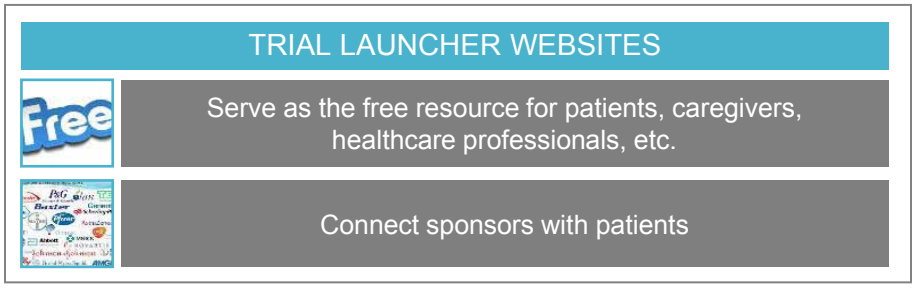


7. Third-party Data e.g. Trial Launcher

Trial launchers are certain commercial web sites that connect sponsors with patients. If a patient considers participating in a clinical trial, he/she can get registered with them, based on their interest in a particular trial.

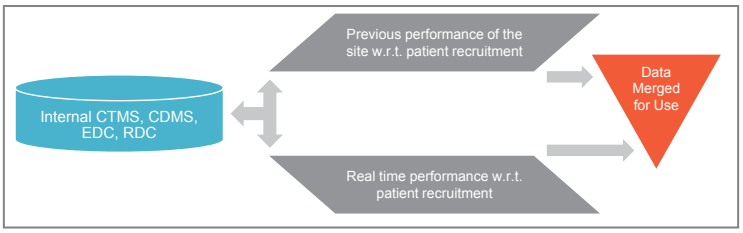
The patient doesn't have to pay them as they get paid for their services by the sponsor. Thus, the trial launchers serve as the free resource for patients, caregivers and healthcare professionals.

When organizations such as trial launchers are introduced to assist in patient recruitment, the patient data will be compiled and matched with the eligibility criteria for the study. The subjects found in line with eligibility criteria will be considered for participation in the study, thereby accelerating patient recruitment.



8. Sponsors Internal Data e.g. EDC, RDC, CTMS, etc.

- Sponsors' internal data from various sources—such as clinical trial management system (CTMS), clinical data management system (CDMS), electronic data capture (EDC) and remote data capture (RDC) can serve as a useful source for extracting information about the site's previous performance in patient recruitment for studies conducted in-house.
- This source can then be integrated with the HCL solution to derive information not only related to the previous performance but also the real-time information about current sites.
- Application of advanced analytics and pattern analysis can deduce information around patient recruitment that can then be extrapolated to predict sites for future trials.



9. Other Methods: Census Data, Prescribing Data, Life , Investigator's Database

Effective use of informatics capabilities can help in testing protocol's feasibility, for its recruitment potential, for range of databases, including -census data, prescribing data, lifestyle data, investigator's in-house data.

By precise use of such databases and mapping methods, geographical areas with high prevalence of disease can be identified. This would help to reach to the right physician's site located in those areas with relevant patients.

10. Recruitment Assistance through Blue Button

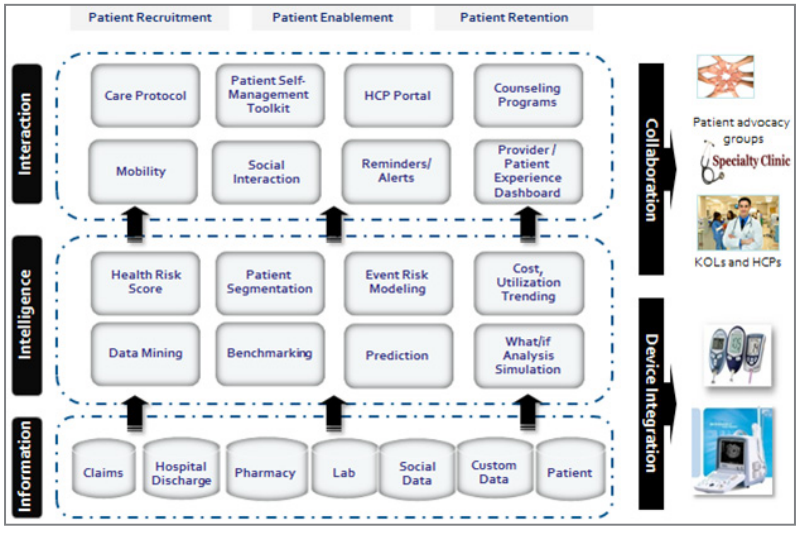
The Blue Button is a symbol for patients to view online and download their own personal health records. Several Federal agencies, including departments of defense, health and human services, and veterans' affairs, implemented this capability for their beneficiaries.[12]

Patient recruitment effort can be further amplified by mapping and matching patient's profiles on Blue Button, shared by them to solution providers.

Sites with the best historical performance can be reached by using epidemiological data to map demographic and disease distributions into geographic clusters, this in turn will help optimize patient recruitment and complete the study faster.

PROPOSED SOLUTION FOR SUBJECT RETENTION

HCL's 3i Framework[13, 14] – Information, Intelligence and Interaction



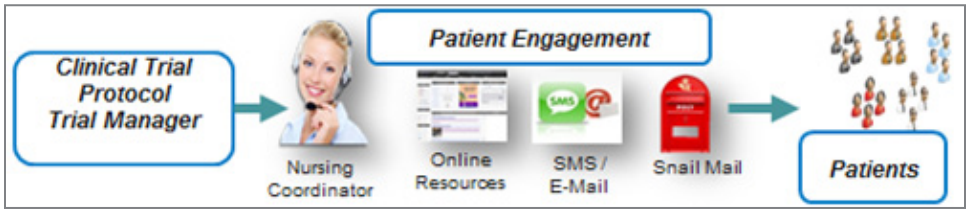
Reference: Internal evaluation, Data on files

Once enrolled, subjects need to be supported with the right information and cared through the right channels for retention and adherence as per the study protocol. Solution frameworks supporting above requirements depend on 1) Information layer to identify the right datasets 2) Intelligence layer to apply the inclusion/exclusion criteria and 3) Interaction layer to retain enrolled patients.

The above platform has the following capabilities:

- Seamless integration of all individual software and medical devices.
- Predictive analysis by effective use of Big-data, and Cloud-based mobility solutions to identify the correct site, patients, etc.
- User-defined and customized dashboards and visualizations to help create matrix of patient enrollment and tracking of prescreened eligible subject.

Patients enrolled in the clinical study will be retained, sustained and supported by numerous channels. They will be provided with online resources/toolkits for self-managed care during the trial



Reference: Internal evaluation, Data on files

Effective communications supported by deployment of correct resource, strategy and technology can ensure the desired number of trial participants and their retention in the study, in a cost-effective manner within the stipulated timeframe.

Retention of study subjects should be viewed as a direct reflection of how much they understand about clinical trial processes and the importance of protocol adherence.[15] Data suggests that more than one-third of all investigative sites conduct research on a part-time basis.[16] This reveals that they may not be giving required time to focus on retention of subjects in a trial once they are enrolled in the study.

To overcome this hurdle HCL has its unique study-specific Patient Enablement Programs (PEP) and Patient Support Programs (PSP). [8]

Highlight of HCL's unique PEP and PSP to support patient retention and adherence as per study protocol[17]

CRM System

- Patient onboarding
- Educating study subjects about the study
- Risk stratification of trials at a study level and pharma/CRO level
- Seamless integration of different systems, e.g., lab data, EMR, EHR data, wearable medical devices, etc.

Portal with application services

- Wireless transmission of medication information—"Smart Labels" medication adherence tracking
- Reminders, referrals, quality of life (QoL) tracking
- Adverse event tracking and alerts

KPO help-desk

- Follows up with patients
- Functions as a 24x7 help-desk for handling queries on trials.
- Help-desk with local language capabilities

Patient enablers: Core team of expert doctors and statisticians

- Works on patient profiling, stratification, and collecting real-timem, compliant data
- Correlates compliance with outcomes and dosing
- Churns data for predictive modeling and analytics
- Analytics for assess adherence/protocol adherence

Integration with patient eDiaries, ePRO, etc.

- Collects information on patient compliance in real time through multilple modes e.g.- patient eDiaries or ePRO, voice, email, web, text messaging, eFax, direct mailing, smartphones, custom devices, etc.
- Caters to a wide range of population

Robust Datawarehouse

- Serves as platform backend
- Automatically collects adherence metrics, summarizes, and generates report in real time

Note: These steps are subject to applicable regulatory approval and may be included as part of the study protocol.

CONCLUSION

The conduct of different trial designs or phases has varying operational needs. It requires a combination of strategies for patient recruitment and retention. As obvious, in absence of these a clinical trial will require rescue site(s) or replacement patient(s) resulting into extension of study timelines and thereby negatively affecting study finances. Incomplete samples imply decreased statistical power and usefulness of its results.[18]

Some of the expected outcomes of implementing the discussed strategy include:

- Meeting all targets of subject recruitment and retention for very challenging trials.

- Improved effectiveness by increased understanding of requirement of patient profile for particular Therapeutic Area (TA).
- Upsurge in automation of various activities of trial conduct such as screening, enrollment, recruitment and visit scheduling.
- The ability of the site to conduct effective research and maintain databank for future use.
- Elimination of unnecessary costs and overheads by avoiding over/under recruitment.
- Decreased subject dropout rate.

Overall, it is suggested that a good protocol design, combined with best practices for recruitment and patient retention will be the mantra for success. In the final run, the overall technological advancement based on evidences extracted from precise mix of above mentioned scientific capabilities, will thus be leveraged. It is expected that this will confidently drive more effective schemes for acquiring and retaining the right clinical study participants.

REFERENCE

1. http://www.pmean.com/11/lasagna.html (http://blog.gobalto.com/2011/10/04/the-site%E2%80%99s-side-patient-recruitment/) (Accessed on: 20th Nov, 2014)
2. http://commons.emich.edu/cgi/viewcontent.cgi?article=1164&context=theses (Accessed on: 20th Nov, 2014)
3. Anderson D.L., A Guide to Patient Recruitment and Retention. Thomson Centerwatch. Chapter 01: page 07; 05;08
4. Anderson D.L., A Guide to Patient Recruitment and Retention. Thomson Centerwatch. Chapter 01: page 03; 266
5. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf (Accessed on: 20th Nov, 2014)
6. Thoma A., Farrokhyar F., McKnight L., and Bhandari M.; How to optimize patient recruitment. Canadian Journal of Surgery. Jun 2010; 53(3): 205–210. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2878987/#b8-1530205) (Accessed on: 20th Nov, 2014)
7. http://management.about.com/od/metrics/a/Measure2Manage.html (Accessed on: 12th July, 2014)
8. HCL's internal data on files. (http://microsite.hcltech.com/unlimit/Unearth.html) (Accessed on: 20th Nov, 2014)
9. http://www.hcup-us.ahrq.gov/databases.jsp (Accessed on: 20th Nov, 2014)
10. McNeil JJ, Piccenna L, Ronaldson K, et al. (2010). "The Value of Patient-Centered Registries in Phase IV Drug Surveillance". Pharmaceutical Medicine 24 (5): 281–288. (http://en.wikipedia.org/wiki/Disease_registry) (Accessed on: 20th Nov, 2014)
11. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=690 (Accessed on: 20th Nov, 2014)
12. "Blue Button | The White House". Whitehouse.gov. Retrieved 2012-04-19. (http://en.wikipedia.org/wiki/The_Blue_Button) (Accessed on: 12th July, 2014)
13. http://www.hcltech.com/lifescience-healthcare/contract-research-organizations (Accessed on: 12th July, 2014)
14. http://www.hcltech.com/lifescience-healthcare/patient-support-program (Accessed on: 12th July, 2014)
15. http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/Patient%2FSubject+Recruitment/The-Patient-Recruitment-Market/ArticleStandard/Article/detail/77707 (Accessed on: 20th Nov, 2014)
16. Anderson D.L., A Guide to Patient Recruitment and Retention. Thomson Centerwatch. Chapter 01: 06.
17. Patient Enablement Programs for Clinical Trial Adherence. http://www.hcltech.com/white-papers/lifescience-healthcare/patient-enablement-programs-clinical-trial-adherence (Accessed on: 20th Nov, 2014)
18. Katrien Oude Rengerink, Brent C Opmeer, et al. Improving Participation of patients in Clinical Trials--rationale and design of IMPACT BMC Medical Research Methodology. http://www.biomedcentral.com/1471-2288/10/85 (Accessed on: 20th Nov, 2014)

HCL LIFE SCIENCES & HEALTHCARE

HCL is a leading provider of Life Sciences and Healthcare Business and Technology services. We are the chosen service provider for enabling new growth drivers for our clients, providing them with industry leading best practices, taking care of their compliance needs and ensuring gold standard process cycle times. Our clientele includes seven of the top ten global pharmaceutical companies, seven of the top ten medical devices companies, six of the top ten health plans, three of the top five CRO's and two of the top three data providers. Equipped with certified technology experts and domain specialists, HCL offers services in critical areas of the life sciences and healthcare eco system such as drug discovery, clinical development, drug safety, regulatory compliance, manufacturing and plant automation, commercial, Healthcare analytics, Population Health Management [PHM], mHealth, member experience management [MEM], fraud, waste and abuse management [FWA].

LET'S CONNECT

Please feel free to write to us at contact.lsh@hcl.com

ABOUT THE AUTHOR

Narender Dureja

Narender Dureja is part of Life Sciences & Healthcare Delivery at HCL, currently designated as Associated Vice President. He has been in the software industry for past 23 years handling Program & Delivery Management, Strategy, Innovation, Consulting and Business Development across industry key verticals; Life Sciences and Healthcare, Compliance, Direct Marketing, Enterprise Resource Planning and Business Analytics.

Nidhi Bajpai

Nidhi has over 14 years' experience in Clinical Research in the Pharma Industry and has worked for all the stages of Drug development. Prior to joining HCL, she was heading Clinical Data Management Department for Panacea Biotec Ltd, New Delhi. She has also worked with organizations such as Novartis and Quintiles in Mumbai.

ABOUT HCL

About HCL Technologies

HCL Technologies is a leading global IT services company working with clients in the areas that impact and redefine the core of their businesses. Since its emergence on the global landscape, and after its IPO in 1999, HCL has focused on 'transformational outsourcing', underlined by innovation and value creation, offering an integrated portfolio of services including software-led IT solutions, remote infrastructure management, engineering and R&D services and business services. HCL leverages its extensive global offshore infrastructure and network of offices in 31 countries to provide holistic, multi-service delivery in key industry verticals including Financial Services, Manufacturing, Consumer Services, Public Services and Healthcare & Life sciences. HCL takes pride in its philosophy of 'Employees First, Customers Second' which empowers its 100,000 transformers to create real value for customers. HCL Technologies, along with its subsidiaries, had consolidated revenues of US$ 5.5 billion, for the Financial Year ended as on 30th September 2014 (on LTM basis). For more information, please visit **www.hcltech.com**

About HCL Enterprise

HCL is a $6.7 billion leading global technology and IT enterprise comprising two companies listed in India – HCL Technologies and HCL Infosystems. Founded in 1976, HCL is one of India's original IT garage start-ups. A pioneer of modern computing, HCL is a global transformational enterprise today. Its range of offerings includes product engineering, custom & package applications, BPO, IT infrastructure services, IT hardware, systems integration, and distribution of information and communications technology (ICT) products across a wide range of focused industry verticals. The HCL team consists of over 100,000 professionals of diverse nationalities, who operate from 31 countries including over 505 points of presence in India. HCL has partnerships with several leading global 1000 firms, including leading IT and technology firms. For more information, please visit **www.hcl.com**

www.hcltech.com

Hello there! I am an Ideapreneur. I believe that sustainable business outcomes are driven by relationships nurtured through values like trust, transparency and flexibility. I respect the contract, but believe in going beyond through collaboration, applied innovation and new generation partnership models that put your interest above everything else. Right now 100,000 Ideapreneurs are in a Relationship Beyond the Contract™ with 500 customers in 31 countries. **How can I help you?**

Relationships™
BEYOND THE CONTRACT

HCL