Clinical Research Trends and New Approaches
Registries from a CRO Perspective

Melinda Urquhart Borrelli
Snr Clinical Project Manager

BASICS OF REGISTRIES

Definition

A PATIENT REGISTRY:

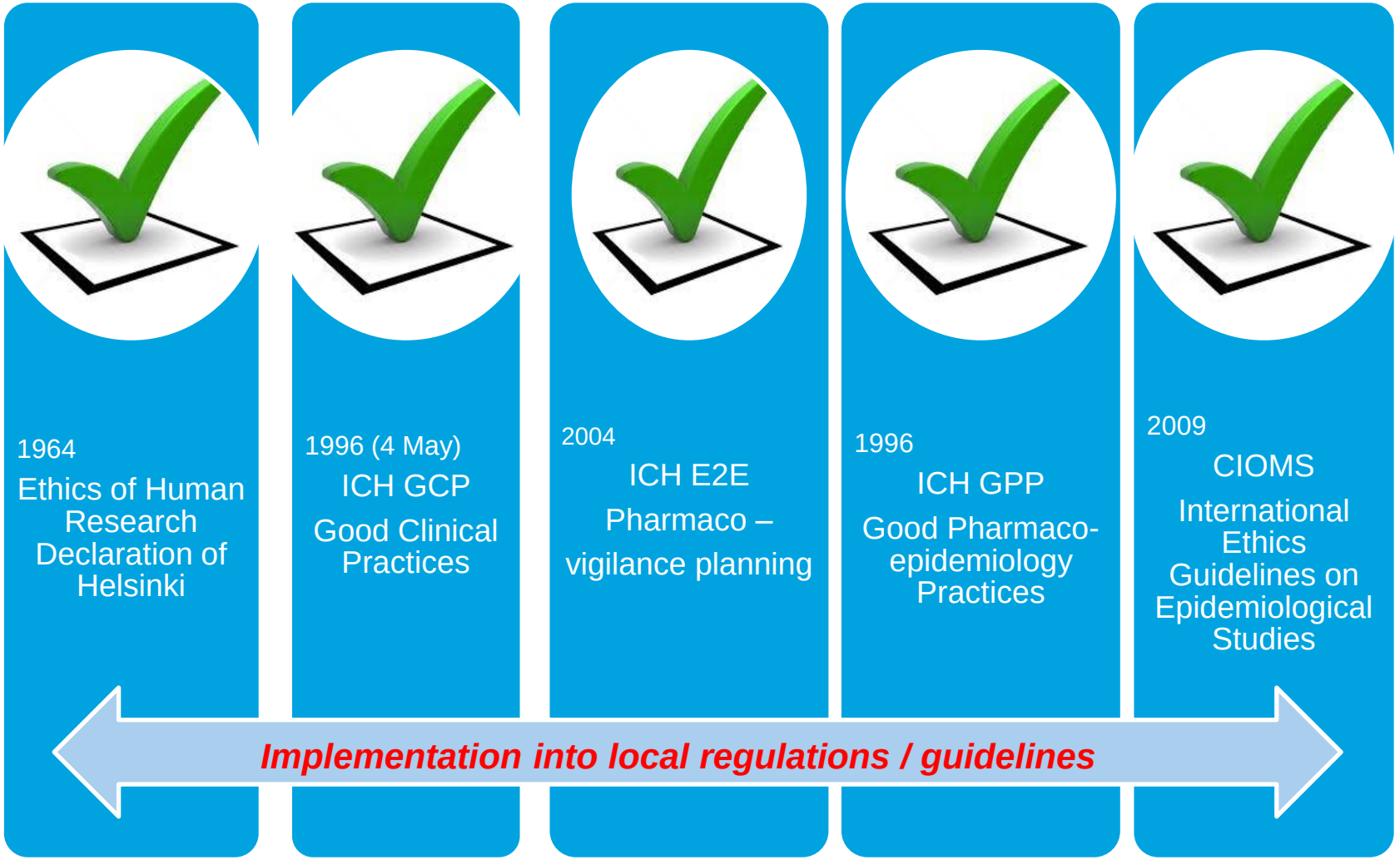
- Is an organised system that uses observational study methods to collect uniform data (clinical and other)
- Evaluates specified outcomes for a population defined by a particular disease, condition, or exposure
- Serves a pre-determined scientific, clinical or policy purpose
- The registry database is the file (or files) derives from the registry

Real-world data defined as everything not collected in Randomised Clinical Trials (RCT).

But in what ways do RCT data and real-world data differ?

BASICS OF REGISTRIES

Regulatory Considerations



Real World Data Fundamentals

Randomised Clinical Trials are not useful for all research

Hypothesis-driven nature of experimental design requires substantial knowledge at the study outset and limits the potential for discovering new information

- Atypical behaviour, patients, and settings
- Protocol-driven behaviour in highly selective patients
- May not be usual physician or usual practice
- Optimal patients should have best outcomes

Do not give insights into why patients and/or clinicians use products as they do or about off-label or risky situations

Also

- Can be hard to recruit patients
- May be small, with imprecise results
- Intermediate endpoints may not be clinically meaningful

Real World Data Fundamentals

What is a patient registry?

Registry-based studies are observational studies

- Diagnostic and treatment decisions are made by the health care provider and patient as they customarily do in real-world settings (not following a protocol for treatment assignment)
- Data can be assembled using existing data, collecting new data, or some combination
- Patients, conditions, care providers and institutions not typically included in Randomised Clinical Trials; for example:
  - Frail elderly, children, pregnancies
  - Community hospitals
  - Less experienced care providers, different training and experience
  - Off label uses result in different populations being treated
- Events with low frequency (rare diseases and rare outcomes); unpredictable diseases (emerging infectious diseases)

Real World Data Fundamentals

What is a patient registry?

- Treatment Characteristics not typically studies in RCTs
  - Adherence, switching and adding
  - On demand treatments administered at home, OTC and other self treatment
  - Con Med dosE tolerance and practical titration
  - Long term use

- Complex Decision Making process
  - About diagnostics
  - By patients and health care providers

- Strong external validity: generalisability
  - Limited inclusion/exclusion means patients are more representative of usual practice
  - Treatment practices including comparative information from actual practice
  - Estimates on impact of treatment are more realistic

Real World Data Fundamentals

Emphasis on Real World Phenomena

Compared to Trails, Real-World Settings offer….	
Reality	Real World practice and outcomes
Applicability	Physician practice and resulting outcomes of that behaviour
Generalisability (external validity)	Limited inclusion/exclusion criteria resulting in diverse study populations, often including many subgroups not traditionally studies in RCT
Availability	Limited number of RCTs relative to the number of decisions that need to be made

Real World Data Fundamentals

Two by two typology of Data Sources

	Retrospective Designs	Prospective Designs
Primary data Collection	**Medical Chart Review**	**Pragmatic Trial** **Cohort Studies** **Health Surveys**
Secondary data Collection	**Administrative Claims** **EMR**	**Automated** **EMR Data Feeds**

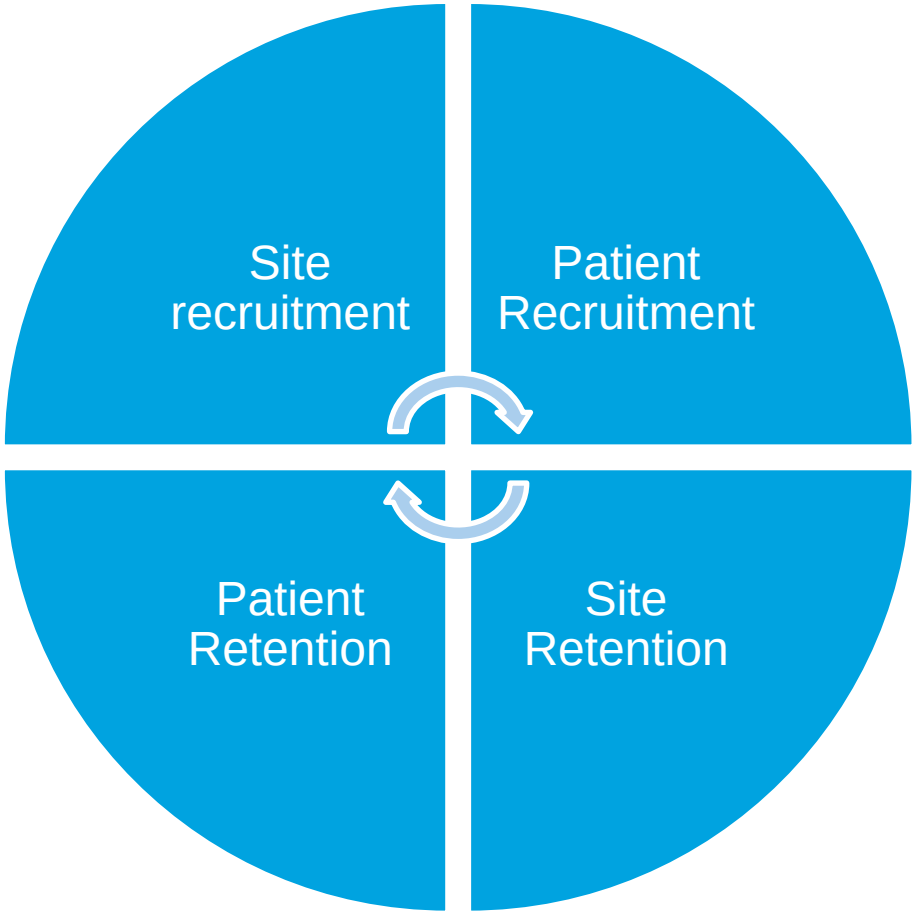
QUINTILES

DESIGN AND USE

Provider & Patient Reported Data

Data Source	Strength & Users	Limitations
Provider Reported 	•More specific and consistent information than available through coded data or medical record	•Clinicians are sensitive to burden •Consistency in capture of certain variables, esp. patient symptoms and use of non prescribed therapy.
Patient Reported 	•Obtain information on treatments not necessarily prescribed by clinicians (e.g., OTCs, herbal meds) •Obtain compliance information •Useful when timing of follow up is not concordant with timing of clinical encounter	•Literacy, language barriers •Need for validated instruments •Loss to follow up, non participation •Ability to report clinical and healthcare utilisation information

Key Success factors



Site Recruitment

Keys to Success

RWLP Research Awareness Campaign	• Educational material / FAQs to research naïve physicians • Investigator / site training
Strategic RWLP Site recruitment Plan	• Include targeted site Qualification Questionnaire • Well constructed key messages on scientific benefits of study • Project team trained in conduct of RWLP, as opposed to traditional RCTs • Note: Some KOLs may not make an excellent investigator and many non KOLs make excellent investigators
Reduce Administrative Burden	• Provide support in obtaining regulatory approvals/contract negotiations • Remote site support
Reduce data Collection Burden	• Provide EDC system that is uncomplicated and easy to use. • Reporting features e.g. • Automated email reminders for upcoming / overdue patient visits • Real time SAE reporting tools to facilitate PV compliance
Attention to sponsor's relationship with sites	• Sponsor review and approve site list • Attention paid to any special considerations for potential sites

Patient Recruitment

Keys to Success

Strategic Patient Recruitment Plan & Tracking	• Active tracking of patient recruitment planned vs actual cohort on site level, includes mitigation and contingency planning • Notification to sites of upcoming and completion of enrolment per cohort • Recommend to have an EDC system that can display enrolment per cohort, allowing real-time tracking and locks enrolment per cohort as soon as target numbers reached.
Make it Easy for Sites	• Easy to use forms to collect and record consent • Local language site support • Ongoing site training • Consider Direct to Patient Contact (D2P)
Make it Easy for Patients	• ICF Template specific to observational study – reduce patient refusal • Limit additional demands on patient time: consider D2P contact • With EC approval, token of appreciation for patients completing questionnaires
Have Alternative Strategies in Place	• Plan B: identify back up sites in a participating country • Plan C: Have additional countries identified as back-up, including countries with higher use of product & facilitated regulatory process.

Site Retention

Keys to Success

Build Sense of Motivation / Make sites feel important	• Personalised messages from sponsor team to individual sites eg milestone achievement • Provide sites with new publications of interest / Newsletters • Timely site reimbursement
EDC system should be able to offer benefits to users	• Patient Management tracking tools and /or data download tool • Possibility to publish and/or present at congress • Use EDC system portal page to share information benchmarking & build sense of community
Make it easy for sites to participate & to collect data	• Support on site by site basis biasing standard of care • Intuitive & focused CRF with well thought out automated audit checks • Support with EC requirements • Data abstraction support
Core Project Team Experience	• RWLP expert project team

Patient Retention

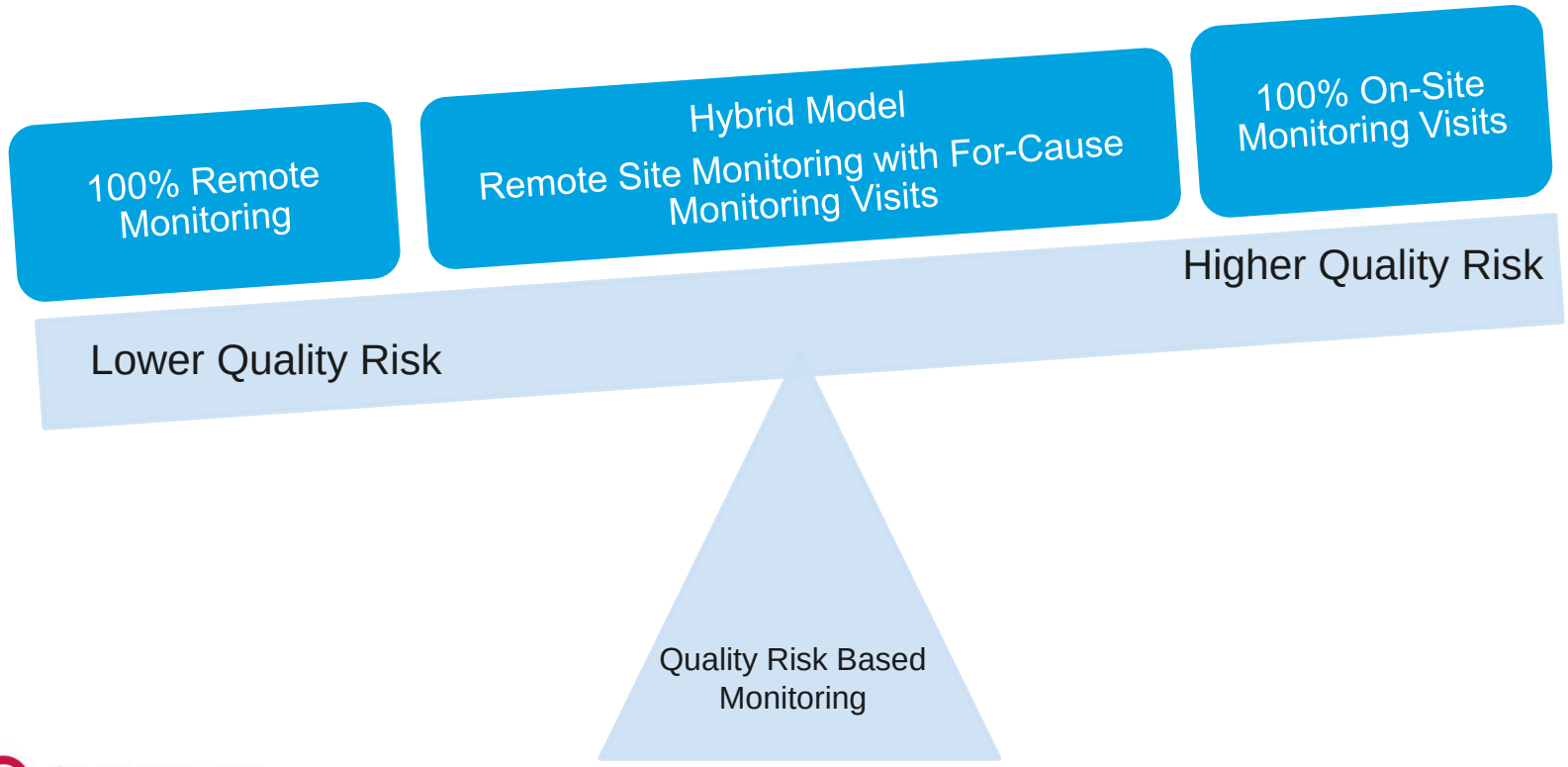
Keys to Success

Minimise number of patients lost to follow up	• Track expected time points for data collection
Support direct to patient contact	• Useful for long term follow up and PROs
Track patient age range	• Plan to re-consent at correct time point and mitigate risk of losing data once patient reaches maturity
Thank the patient	• Acknowledge patient contribution

QUINTILES

Monitoring – A different Approach

Quality Risk Based Monitoring



QUINTILES

Quality Risk Based Monitoring Principals

Two fold approach

Centralised Remote Monitoring

(Conducted to pre-empt a quality risk)

- QRs are pre-identified during study development
  - Missing/ erroneous data, delay in data entry, unanswered queries, repeated errors, incomplete/delay in SAE reporting
- If QR identified during centralise monitoring an alert is triggered

On-Site For-Cause Monitoring

(conducted to mitigate and/or address an identified high level quality risk)

- For-cause site monitoring activities include but not limited to:
  - Review of Informed Consent
  - Source data verification
    - 100% study endpoints
    - 100% SAE's
- On-site training
- Addressing issues/concerns
- Motivating sites

QUINTILES

Challenges

Inadequate Informed Consent

- Informed Consent not conducted according to GCP/GPP requirements
- Examples:
  - › Patient taking consent home and signing
  - › Patient and Investigator signing consent form at different times.
  - › Consent not documented in source notes

Example Scenario:

Patient is seen for their routine treatment approximately every 3 months. Discussion around commencing treatment with drug under investigation in observational study is discussed with patient. Patient goes home to consider their treatment options and is provided the study informed consent form to review as well.

Patient decides to start treatment with study drug and phones site to advise of decision. Investigator mails out prescription to patient. Patient starts treatment.

Patient signs the informed consent form at home and returns the form to investigator at their next visit. Investigator then signs consent form.

Challenges

Inadequate Informed Consent cont.

Strategies

- Document site specific informed consent process (Standard Operating Procedure – SOP)

- Notify Ethics Committee of SOP seeking approval

- Informed consent waiver
  - › Only applicable in special circumstances

- Consent taken over phone/skype

Challenges

Electronic Data Entry

EDC system – design

› Most EDC system are overly complicated for observational research needs.

› Single data entry, collect only what is really needed

› EDC designed especially for observational studies (Infosario Outcome)

Challenges

Lack of Support for Risk Based Monitoring

- Expectations for on-site monitoring based on early phase experience

- Better understanding of the objective of RWLP (registries) will help appreciate Risk Based Monitoring
  - › Only data collection
  - › There is no study mandated procedures
  - › Patient treatment completely independent of study protocol

- Quality Risk – Based Monitoring enables focused attention of risk, while promoting efficient utilisation of time, resources and budget

- Applying the integrated approach of Risk Based Monitoring in conjunction with procedures, such as investigators training and written guidance can assure appropriate conduct of a post-approval study in accordance with ICH-GCP and/or GPP Guidelines.

Challenges

Misc.

- Lack of interest from sites
  - Similar amount of work to set up site as early phase studies with no immediate results
- Research naïve sites
  - Phase IV study sites are not always experienced research centres.
  - No study coordinator or research nurse
  - Additional support and training required
- Data collection
  - Site team structure does not include study coordinators, no resources for data entry.
  - SMO services required – Quintiles is investigating this type of service for Australian sites. Already common in other Asia Pacific countries.

QUESTIONS??