# Recent Innovative Approaches and Requirements for New Product Development

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# Recent Innovative Approaches& Requirements

- Master Protocols
- Adaptive Designs
- Risk-Based Monitoring – Statistical Approaches
- Publication of Clinical Data – Anonymization
- Pragmatic Randomized Clinical Trials
- Mobile Technology Derived endpoint in Clinical Trials

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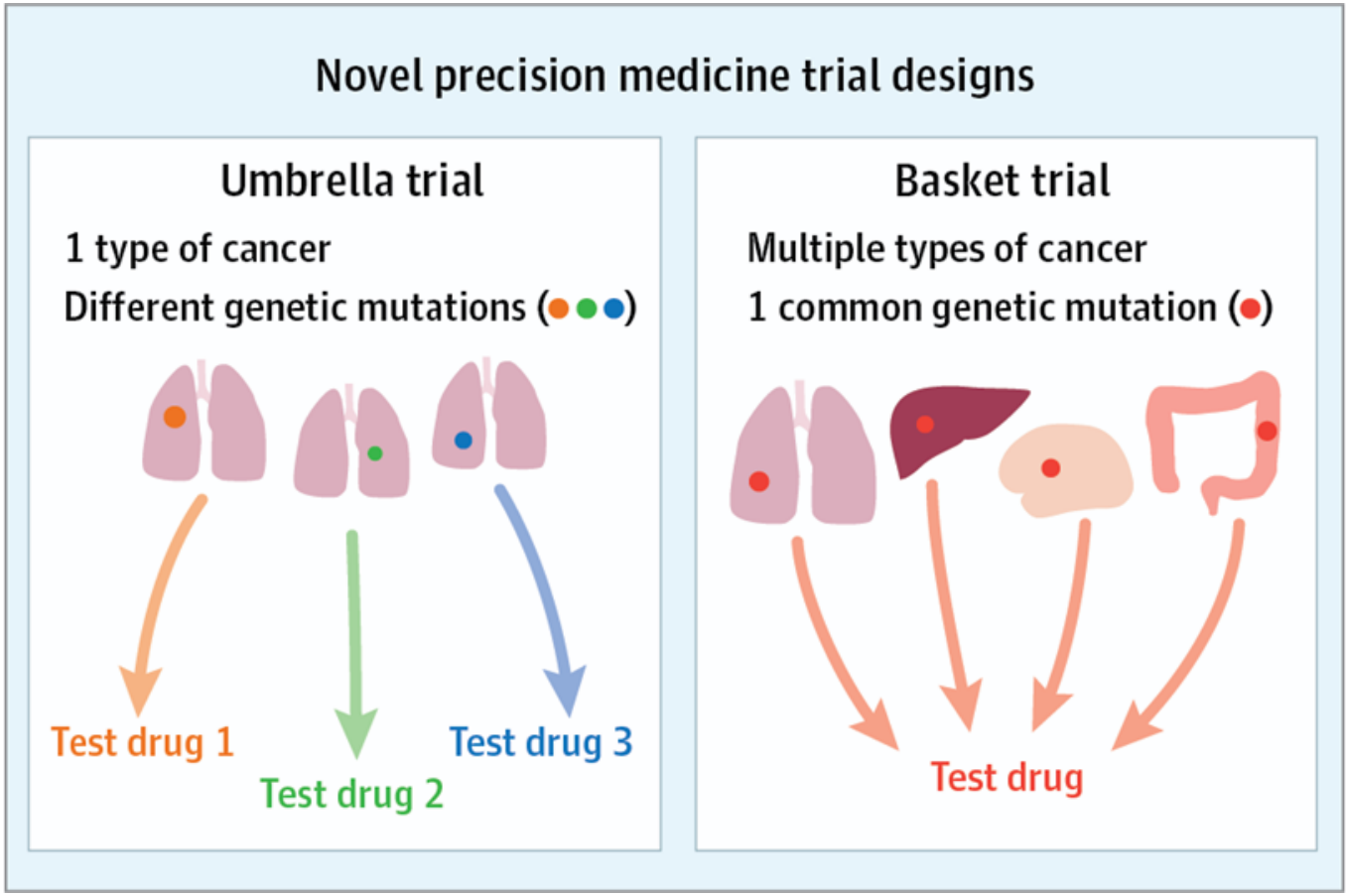
# Master Protocols

| Trial Type | Definition | Examples |
|---|---|---|
| Basket | A protocol employing a targeted therapy for multiple diseases. The trials could contain multiple strata testing various biomarker drug combinations. | NCI MATCH<br>NCI MPACT<br>SIGNATURE<br>CREATE |
| Umbrella | A protocol with more than one targeted therapy studied for a single disease. Select patients are screened for the presence of a biomarker or other characteristic(s) and then assigned to a study arm accordingly. | BATTLE<br>I-SPY2<br>LUNG-MAP<br>FOCUS4 |
| Platform | A protocol employing multiple therapies for a single disease, with therapies allowed to enter/exit based on the decision algorithm | Dian-TU |

Woodcock and LaVange, “Master protocols to study multiple therapies, multiple diseases, or both

# Master Protocols

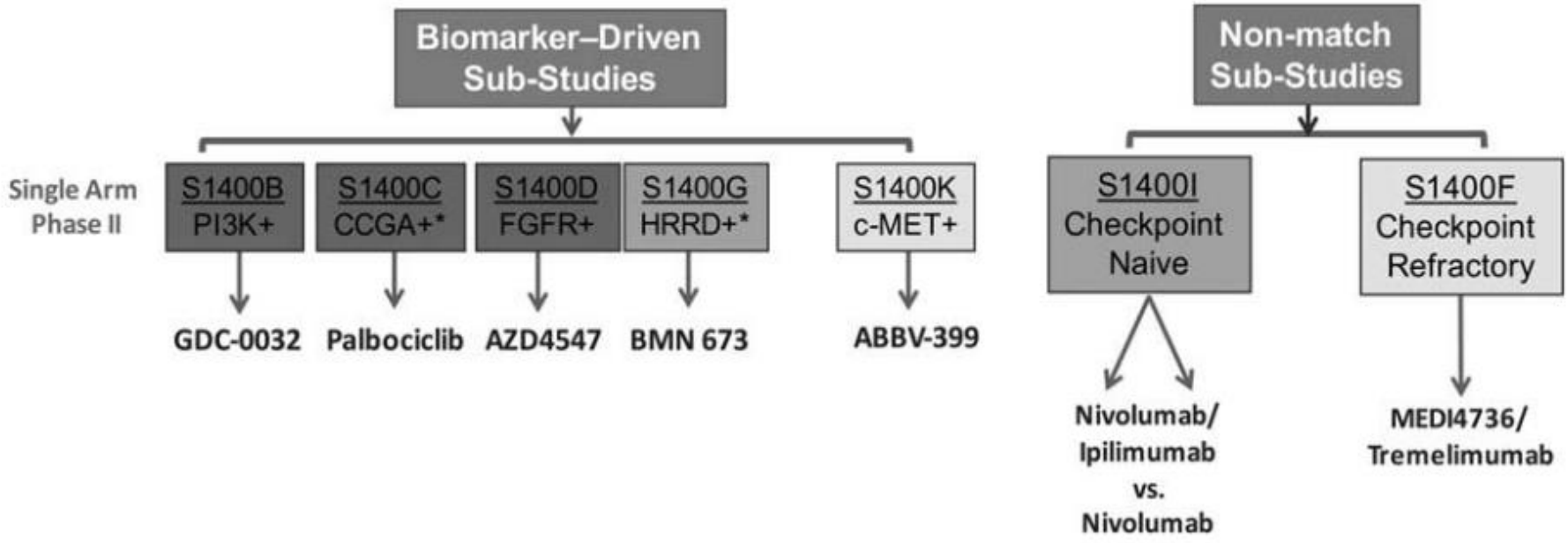



West H. Novel Precision Medicine Trial Designs: Umbrellas and Baskets. *JAMA Oncol.* 2017

# Master Protocol In Lung Cancer

## Lung Master Protocol (Lung-MAP) — A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400

The biomarker-driven, a phase II/III **umbrella-design trial**, which initially launched in 2014, previously enrolled patients with advanced-stage squamous cell lung cancer. It was originally designed to evaluate **4 novel targeted agents** and one immunotherapy agent compared with standard-of-care regimens in separate, randomized substudies.




*As of June 2017*

Master protocols in lung cancer: experience from Lung Master Protocol (2018)

# Lung-MAP

- Initially 3 parallel randomized phase II/III sub-studies for targeted therapy vs. SOC (docetaxel)

- Phase II endpoint: PFS (68-124 patients per sub-study)
- Phase III endpoint: Overall survival(OS) with phase II patients contributing (272-336 patients per sub-study)

- One cohort (c-MET) closed early for toxicity; reopened 2018

- March 2015: FDA approved nivolumab in same patient population
  - Control arm: docetaxel no longer the standard of care

- Lung-MAP re-opened with modifications:
  - Control arm dropped in phase II --> single arm only
  - Non-match arm: single vs combo immunotherapy

*www.lung-map.org*

# Adaptive Designs for Clinical Trials

By **adaptive design** we refer to a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.

*Gallo (PhRMA Working Group) 2006*

A study design is called "adaptive" if statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an interim analysis **with full control of type I error**.

*European Medicines Agency 2007*

... an adaptive design is defined as a clinical trial design that allows for **prospectively** planned **modifications to one or more aspects** of the design **based on accumulating data** from subjects in the trial.

*US FDA 2018*

# Flexible Sample Size Re-Estimation Design

An adaptive design that allows for sample size adjustment or re-estimation based on the observed data at interim

Initial trial design stage:

- Sample size assumptions based on information available
- Uncertainty in assumptions
- Potential for unpowered study

Nuisance parameters to be re-estimated

- e.g. standard deviation, event rate, coefficient of variation, drop-out rate
- using internal data at an interim analysis, adjust final sample size

The sample size review should be conducted blinded manner:

- Preserves the Type I error of the trial
- Will not compromise the integrity of the trial

# Most Popular Adaptive Designs

- Adaptive randomization design
- Group sequential design
- Flexible sample size re-estimation design
- Drop-the-losers (pick-the-winner) design
- Adaptive dose finding design
- Biomarker-adaptive design
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- Two-stage phase I/II (or II/III) adaptive design
- Multiple adaptive design

# Submission Success of Adaptive Design Trials (n=78)

| Type of Adaptive Design | Cleared | Cleared With Resubmission[a] | | Limited Clearance[b] |
|---|---|---|---|---|
| Adaptive randomization | 3 | 2 | Request of independent statistical analysis plan | |
| Adaptive sequential design | 5 | 2 | Justification of timing and frequency of interim analyses | |
| Sample size re-estimation | 6 | 2 | Control of inflation of type I error | |
| Pick the winner / drop the loser | 12 | 1 | Definition of efficacy and safety targets for futility | |
| Adaptive dose progression | 12 | 3 | Adjustment of therapeutic dose regimen | |
| Phase II/III "seamless" | 16 | 2 | Control of inflation of type I error due to inflation of sample size | |
| Biomarker adaptive design | 1 | 1 | Request of further information for biomarker validation | 1 |
| Endpoint adaptation | | 1 | Redefinition of rationale from superiority to non-inferiority | 1 |
| Change in study hypothesis/objective | 4 | 2 | Redefinition of rationale and therapeutic endpoints | 1 |
| Total | 59 | 16 | | 3 |

*a, b: FDA requirement*
*n=78, published between 2006 and 2017*

Cerqueira, F. P., Jesus, A. M. C., & Cotrim, M. D. (2019). Adaptive Design: A Review of the Technical, Statistical, and Regulatory Aspects of Implementation in a Clinical Trial. Therapeutic Innovation & Regulatory Science.

# Clinical Monitoring – Risk Based Approach

- Trial Management/clinical monitoring cost are huge expense
  - to achieve data quality
  - to monitor patient safety
  - to have reliable study data for regulatory submission

- 100% source data verification (SDV) by CRA at each site on regular intervals (every 4-10 weeks) are costly, time consuming, difficult to identify issue pattern across subjects or visits

- FDA published the final guidance document “Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring” in August 2013

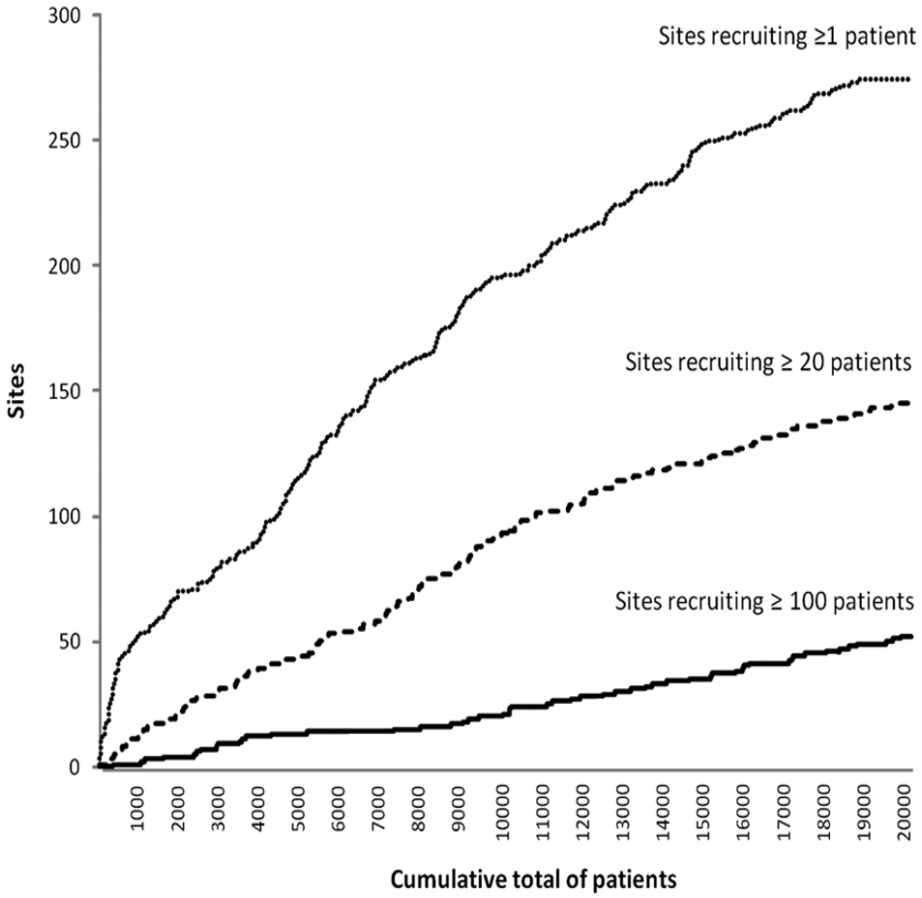
*Describes strategies for monitoring activities that reflect a modern,* ***risk-based approach*** *focusing on critical study elements, and relies on a combination of monitoring activities to oversee a study* effectively.

# Risk Based Monitoring – Statistical Approaches

- Risk-Based approach require to define thresholds for data review, which may be subjective and fixed
- Recent addendum ICH E6 R2 Good Clinical Practice (Nov 2016), section 5 on risk and extent and nature of monitoring highlight and recommended an increased need for **Risk-Based Monitoring(RBM)** and **Centralized monitoring(CSM)**
- Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians)
- Centralized Monitoring - Statistical Applications
  - Identify critical data points for each study protocol with Statistical and Medical input
  - Develop and validate appropriate statistical models
  - Analyze accumulating study data using appropriate statistical models and identify risk indicators (SAEs reported, Number of dropouts etc.,.)
  - Focus monitoring efforts and corrective actions on risk indicators, subject level or site level
  - These data driven approaches& efforts ensure data quality
  - These Statistical models can run at regular intervals, as when needed till study completed
- Recently few pharma companies setting up centralized statistical functional team and new SOP for study Biostatisticians and statistical programmers responsibilities

# Central Statistical Monitoring : Example

*High recruitment early in the trial*

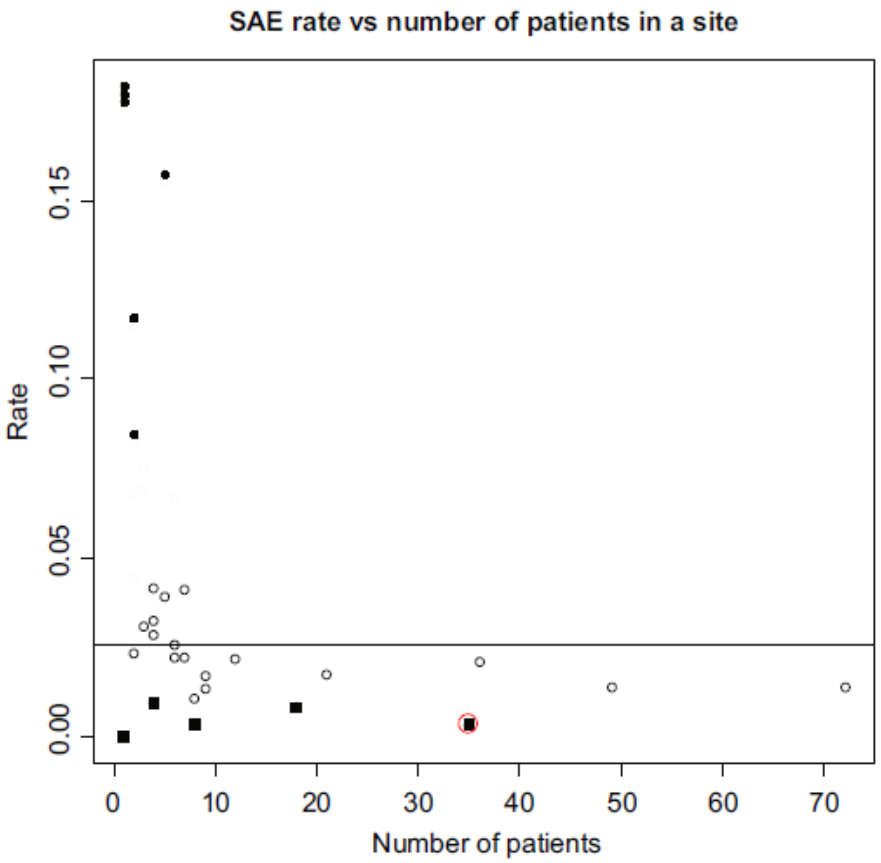



- CRASH-2: Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage.
- Accumulation of sites in the CRASH-2 trial as the target sample size of 20,211 patients was achieved.
- Central statistical monitoring showed a low case fatality rate (less than 1%) and that most patients had baseline physiological measures that were within a normal range.
- After all investigations at sites and discussions with investigators it was figured out that further guidance required for the fundamental inclusion criterion ‘ongoing significant haemorrhage’

Central and statistical data monitoring in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial (2013)

# Central Statistical Monitoring : Example

*Sites under reporting AE/SAE*




- SAE rates for each site are calculated as the number of patients with an SAE divided
- by the number of patients and time in the trial

- The sites with zero SAEs, plus the lowest 10% of rates are shown as black squares

- The circled black square is the fabricated site, recruited 35 patients and recorded only 6 SAEs for 35 months in the trial

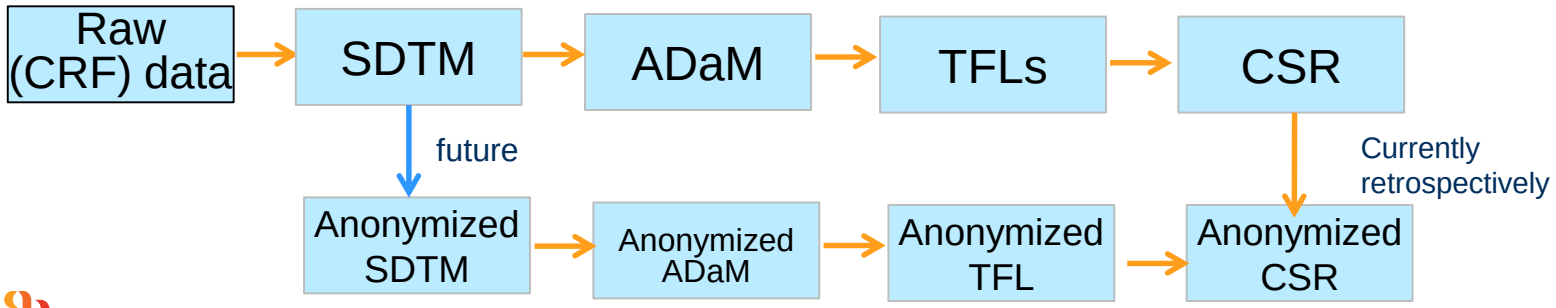
Application of methods for central statistical monitoring in clinical trials (2013)

# Compliance with EMA Policy 0070 on the External Publication of Clinical Data

Secondary use of individual patient data for health research plays an increasing role in modernizing our healthcare systems, driving medicines innovation and fostering better patient outcomes. Pharma is accessing an unprecedented depth and breadth of clinical data. This significantly expands research potential, but also creates re-identification risks.

Anonymization is the process of turning data into a form that does not identify individuals and where identification is not likely to take place. It allows for a much wider use of the information.

EMA Policy 0070 is composed of two phases.
Phase 1 entered into force on 1st January 2015 and pertains to publication of **clinical reports only.**
Phase 2, which will be implemented at a later stage, pertains to the publishing of **individual patient data (IPD)**. Clinical reports and IPD are collectively referred to as “clinical data”



# Anonymization Process

Recommended anonymization(De-identification) process steps -

1. Determination of direct identifiers and quasi-identifiers
2. Identification of possible adversaries and plausible attacks on the data
3. Data utility considerations
4. Determining the risk of re-identification threshold and evaluation of the actual **risk of re-identification**
5. Anonymization methodology
6. Documenting the anonymization methodology and process

**Anonymization report** to be submitted to the Agency together with the **anonymized clinical reports**

The report should contain information, (i) The anonymization process, including the methodology (techniques used and the rationale for using them), (ii) Outcome of the analysis of the risk of re-identification or alternatively confirmation that the three criteria (singling out, linkability and inference, or perform a risk assessment) for anonymization have been fulfilled

The EMA suggests 9% as an acceptable risk of re-identification threshold

Anonymization process and anonymized datasets, CSR and report will be review required by Biostatisticians and statistical programmers. Many tools have been developed for these clinical data anonymization process. Ex.. ARARA, Shadow etc.,.

# Pragmatic Randomized Clinical Trials

Pragmatic Randomized Clinical Trials combining real-world evidence and randomization, are used to inform treatment effectiveness and healthcare decisions

Key design elements of a pragmatic randomized clinical trial

- Real-world population (patient population in practice)
- Real-world setting (practitioners and community sites)
- Appropriate comparison arm (active control arm)
- Relevant outcome (derived also from EHRs which support treatment decision)

Use of alternative data collection approaches may lead to uncertainties, and absence of blinding could potentially lead to non-random missing data at study endpoints such that randomization is no longer protected by an **intent to treat**. More complex randomization strategies may be needed to minimize bias.

Examples of Pragmatic Randomized Clinical Trials,
Pragmatic RCT Comparing Aripiprazole, Olanzapine and Haloperidol in the Treatment of Schizophrenia

A Cluster-randomized, Pragmatic Trial of Hemodialysis Session Duration

A Comparative Effectiveness Study of Major Glycemia-lowering Medications for Treatment of Type 2 Diabetes

# Mobile Outcome Assessments

## *Therapeutic Areas By study Design*

| | Interventional trials ($n$ = 22) | | Observational studies ($n$ = 66) | |
|---|---|---|---|---|
| | $n$ (%) | Ref. | $n$ (%) | Ref. |
| *Therapeutic area* | | | | |
| Cardiology | 3 (14) | 17, 19, 25 | 16 (24) | 31, 37–40, 53–63 |
| Diabetes | 5 (28) | 11, 12, 24, 26, 28 | 8 (12) | 30, 31, 41, 64–68 |
| Sleep | 3 (14) | 15, 20, 21 | 7 (11) | 32, 34–36, 69–71 |
| Obesity | 0 (0) | – | 9 (14) | 30, 72–79 |
| Geriatrics | 0 (0) | – | 9 (14) | 80–88 |
| Neurology | 1 (5) | 13 | 3 (5) | 44, 46, 89 |
| Reproductive and peripartum health | 2 (9) | 8, 10 | 2 (3) | 90, 91 |
| Orthopedics | 1 (5) | 22 | 3 (5) | 92–94 |
| Pulmonology | 0 (0) | – | 3 (5) | 95–97 |
| Arthritis | 1 (5) | 16 | 2 (3) | 93, 98 |
| Psychology | 0 (0) | – | 3 (5) | 78, 99, 100 |
| Cancer | 3 (14) | 14, 18, 23 | 0 (0) | – |
| Nephrology | 0 (0) | – | 2 (3) | 33, 101 |
| Gastroenterology | 1 (5) | 29 | 1 (2) | 43 |
| Nutrition | 1 (5) | 27 | 1 (2) | 32 |

Ref. Use of Mobile Devices to Measure Outcomes in Clinical Research, 2010–2016: A Systematic Literature Review (2018)

# Mobile Outcome Assessments

## *Mobile Technology By study Design*

| | Interventional trials ($n$ = 22) | | Observational studies ($n$ = 66) | |
|---|---|---|---|---|
| | $n$ (%) | Ref. | $n$ (%) | Ref. |
| *Device* | | | | |
| Wearable inertial sensor/accelerometer | 16 (73) | 8, 9, 12, 14–25, 27 | 59 (89) | 30, 32–36, 44, 46, 53–103 |
| Biosensor | 6 (28) | 11, 12, 24, 26, 28, 29 | 7 (11) | 31, 33, 37, 39–41, 43 |
| Continuous glucose monitor | 5 (23) | 11, 12, 24, 26, 28 | 1 (2) | 41 |
| Electrocardiograph | 0 (0) | – | 2 (3) | 31, 40 |
| Ingestible pH monitor | 1 (5) | 29 | 1 (2) | 43 |
| Ambulatory blood pressure monitor | 0 (0) | – | 1 (2) | 39 |
| Implantable cardioverter-defibrillator | 0 (0) | – | 1 (2) | 37 |
| Heart rate monitor | 0 (0) | – | 1 (2) | 33 |
| Pressure sensor and instrumented walkways | 1 (5) | 13 | 1 (2) | 38 |
| Medication adherence monitor | 1 (5) | 10 | 0 (0) | – |
| Geolocation monitor | 0 (0) | – | 1 (2) | 33 |
| Global Positioning System | 0 (0) | – | 1 (2) | 33 |
| Altimeter | 0 (0) | – | 1 (2) | 33 |

Ref. Use of Mobile Devices to Measure Outcomes in Clinical Research, 2010–2016: A Systematic Literature Review (2018)

# Mobile Technology-Derived Endpoints in Clinical Trials

| SPECIFIC BENEFITS | | | |
|---|---|---|---|
| | SHORT-TERM | MEDIUM-TERM | LONG-TERM |
| Patient Centricity | Development of high-quality, patient-centric, mobile technology-derived endpoints | Greater use of endpoints that matter to patients in clinical trials<br>Reduced participation burden (patient and caregiver) in clinical trials<br>Fewer barriers to trial participation<br>Larger, more inclusive, and more generalizable trials | Increase in clinical trials that yield more complete information on how therapies affect aspects of disease most important to patients<br>Increase in clinical trials that yield better information to inform regulatory and labeling claims as well as subsequent reimbursement decisions<br>Increase in participation and retention of patients in clinical trials through the development and selection of measures that matter to patients |
| Efficacy | Inclusion of mobile technology-derived endpoints in early-phase trials and in postmarket surveillance | Improved predictability rates for advancement from phase II to phase III trials<br>Increased efficiency of postmarket surveillance | Increase in number of potentially successful treatments taken forward for testing in phase III trials, particularly in high-risk therapeutic areas |
| Efficiency | Generation of data needed by payers to make coverage determinations during clinical trials | Prevention of delays in coverage, payment, and use decisions | Prevention of delays in patient access to therapies |

Source: Clinical Trials Transformation Initiative's Mobile Clinical Trials - Novel Endpoints Project
Clinical trial is used here to refer to studies done to support regulatory approval for marketing

# Summary

Master protocols, a collaborative approach to drug development focus on disease, can help improve the quality of evidence, and cut down research cost and time.

Adaptive trial designs various approaches allow us to develop shorter and cheaper trials while maintaining statistical validity thus bringing life-changing therapies more quickly with lower costs

Centralized Statistical Monitoring is an integral part of risk based approach to monitoring of clinical investigations. Multi-disciplinary team to define the monitoring framework for the protocol and determine the clinical relevance of statistical findings through out the trial conduct

Risk of Re-Identification of Patient-Level Data should be eliminated when sharing clinical data accordance with EMA policy 0070

Pragmatic Randomized Clinical Trials are much useful to understand the effectiveness of treatments in real world setting, should consider address common design issues like randomization and blinding

Mobile technology in clinical trials for regulatory submission can be further adopted and used by developing evidence-based novel endpoints and validated technologies

# References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