PCMG October Workshop

29 October 2020

Accountability & Delivery | Collaboration | Partnership | Integrity

Today's Topics

- Defining decentralized trials
- When to use a decentralized approach
- Example of how to use
- Decentralized Ecosystem – technology and patient support
- Contracting and other considerations

Decentralized Clinical Trial - Defined

Traditional
All patient visits are on-site

Hybrid
Mix of traditional on-site patient visits and remote visits conducted by home health and telemedicine

Fully Decentralized
No physical on-site patient visits, all remote visits conducted via telemedicine and/or phone

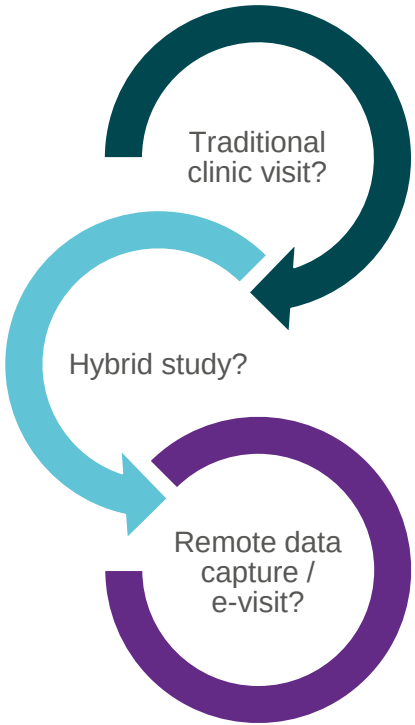
Patient visits on-site
Collection of data by investigator and site staff

Direct to Patient
Collection of data directly from patients by wearables, sensors, diaries and/or Direct to Patient Contact (DPC) solutions

Hybrid trials can be implemented across all phases of studies and most indications

Evaluating when to deploy a decentralized approach

Important to assess feasibility of conducting a decentralised study visit



- **Therapeutic area/endpoint types**
  - Endpoints conducive to being measured, or confirmed, remotely. For example:
    - Digital endpoints (wearable, ePRO, etc.)
    - Readily recorded endpoints (hospitalization, pregnancy, death, etc.)
    - Can record/observe via telemedicine (rash, fever, etc.)
    - Can collect via home-health visit or similar (blood pressure, blood draw, etc.)
- **Study design**
  - Non or low - interventional studies are often well-suited for decentralised approach, depending on endpoints to be collected
- **Study drug**
  - Easy to administer (especially if self-administered)
  - No special storage requirements/not a controlled substance (etc.)
  - Well-characterized safety profile
- **Subjects and follow up**
  - Patients with hindered mobility
  - Rare disease studies, where patients are scarce and geographically remote
  - Long-term studies requiring extended follow-up (e.g., 12 months post-hospitalization for recurrence of cardiovascular endpoint such as ACS, 5-year incidence of pregnancy for LARC, etc.)
- **Regulatory considerations**
  - Study conducted in country/region where telemedicine is allowed and used, eConsent is allowed, etc.

Remote or decentralised approaches are especially well-suited for non or low interventional studies

Hybrid studies (combination of traditional clinic visits and remote visits) can be implemented in almost all types of studies

What Do Patients Think About Decentralized Trials?

Web Based Survey to the ICON Global Site Network (US and EMEA)
Over 4,000 Respondents in ~2 Weeks

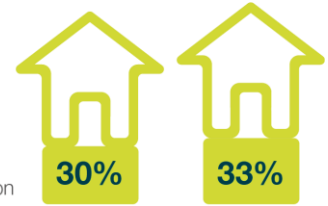
Clinical trial experience

Had participated **43%** Had not participated **57%**

Varied Therapeutic Areas
Highest percentages
in **Vaccines**, **Cardiovascular**, **Rheumatology**, **Pulmonology**

Where would you prefer study **visits to take place?**

Majority indicated **hybrid** or **no preference** in location



Hybrid | No preference

Would you consider **participation** in clinical trials where all **visits** were conducted **virtually via video calls?**

57%Yes

Where would you prefer **clinical trial tests to be taken?** (Blood samples, vitals signs)

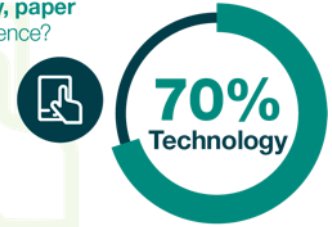
Majority indicated hybrid or no preference

Do you prefer **in-person** interaction with site staff during visits even if **more travel** and **inconvenience?**

40% yes / **40%** no preference

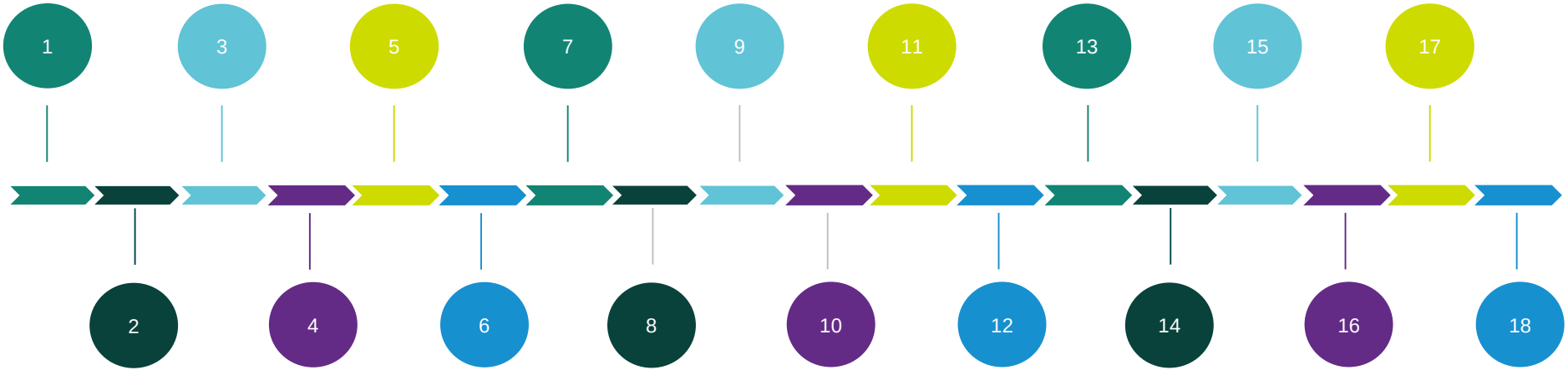
Even split

Patient diaries preference – **technology, paper** or no preference?



Lupus Nephritis – Traditional On-Site Model

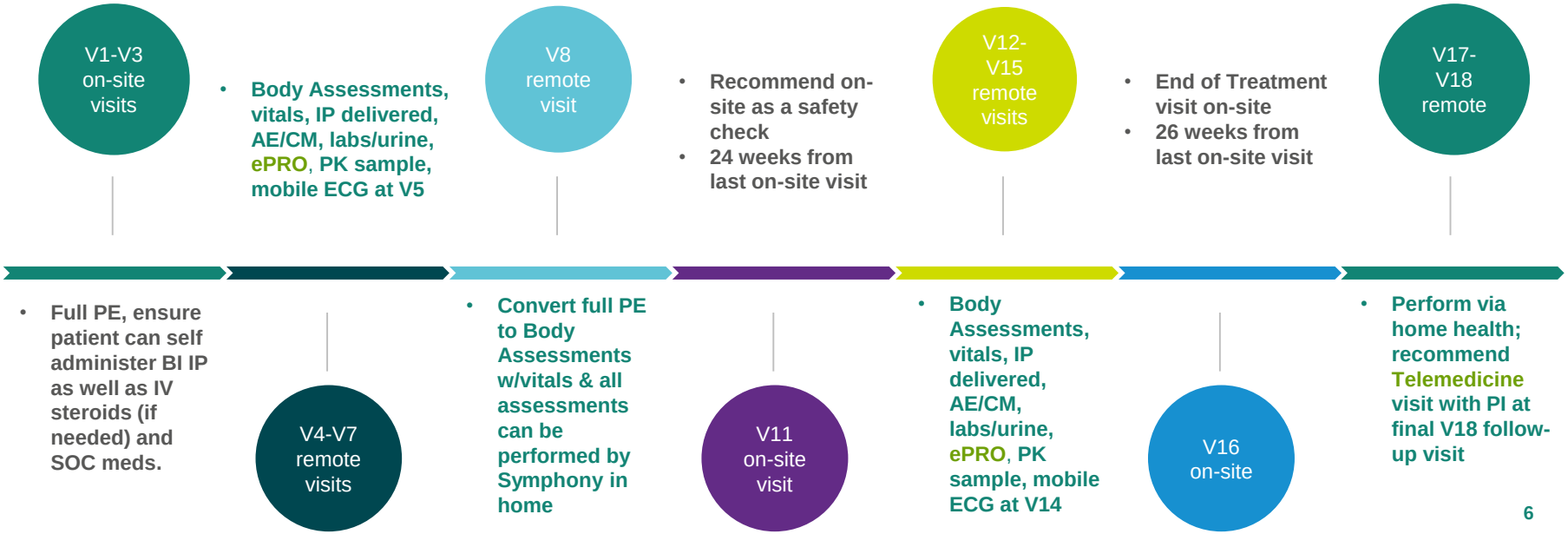
- 22 countries, likely informed based on location of local affiliates
- 120 randomized patients
- ~5 patients per site if 1 site/country
- Study includes a minimum of 18 on-site visits
- Assessments include PE, IP, vitals, AE/CM, labs/urine, ePRO, PK sample, ECG and optional renal biopsy
- 52 weeks of treatment
- 8 weeks of follow-up



Lupus Nephritis – Hybrid Model

- Digital recruitment strategy by ICON = Recruit Patients Faster
  - Supported via NORA
- ICONs PMG, Medinova & Healthcare Alliance PIs for rapid = Reduced Timelines
- Symphony to conduct remote visits = Increased Patient Satisfaction & Retention
  - Supported via NORA

- ePROs supported by NORA – programmed to be administered in order per protocol & prior to drug dosing to ensure compliance = Reduced Patient & Site Burden
- NORA to send reminders to patients for drug dosing, tapering of SOC, questionnaire completion = Increased Compliance & Retention
- ICON Direct to Patient Contact (DPC) follows up on reminders w/patient = Increased Compliance and Retention



Patient Insights – *When, what for and how?*

- We strongly believe that ***anytime is the right time*** for insights work.
- Engaging directly with patients, care-partners and other key voices in the patient's journey, you will be able to leverage findings across the continuum of drug development
- Import to identify the business need driving the need for insights?

Protocol Design

Identify barriers and motivators for patients based on study design and make recommendations on feasible changes

Outreach & Recruitment

Guidelines for development of recruitment and retention tactics that consider the age range of participants and countries

The most effective ways to communicate with patients (sending the right messages, at the right time, via optimal channels).

Consent & Site Visits

Potential protocol barriers and recommendations for mitigating these barriers.

Recommendations for site training to support consent and completion of the study.

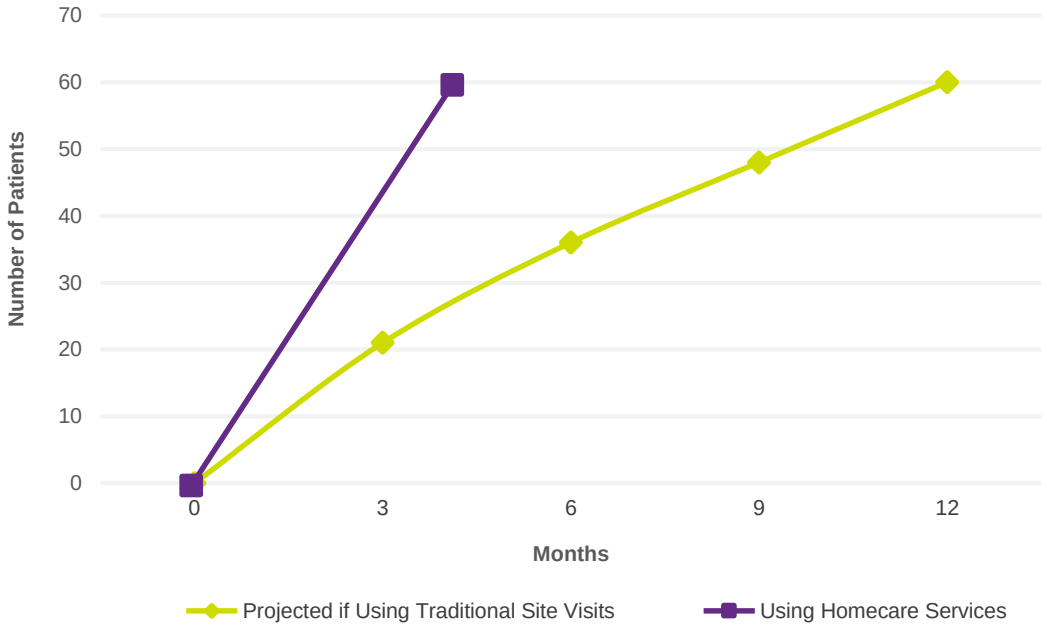
Study Retention

Patient Retention recommendations that include educational content, tactics and tools that will resonate with patients and care-partners.

METHODOLOGIES

Case Study In-Home Services - Accelerated Patient Recruitment

Increased Enrollment:
Actual enrollment using homecare services vs. projected enrollment timelines



8 MONTHS SAVED
in expected enrollment time

Study start delayed by 11 months, but **COMPLETED ENROLLMENT AHEAD OF SCHEDULE**

100% OF PATIENTS
enrolled within 4 months

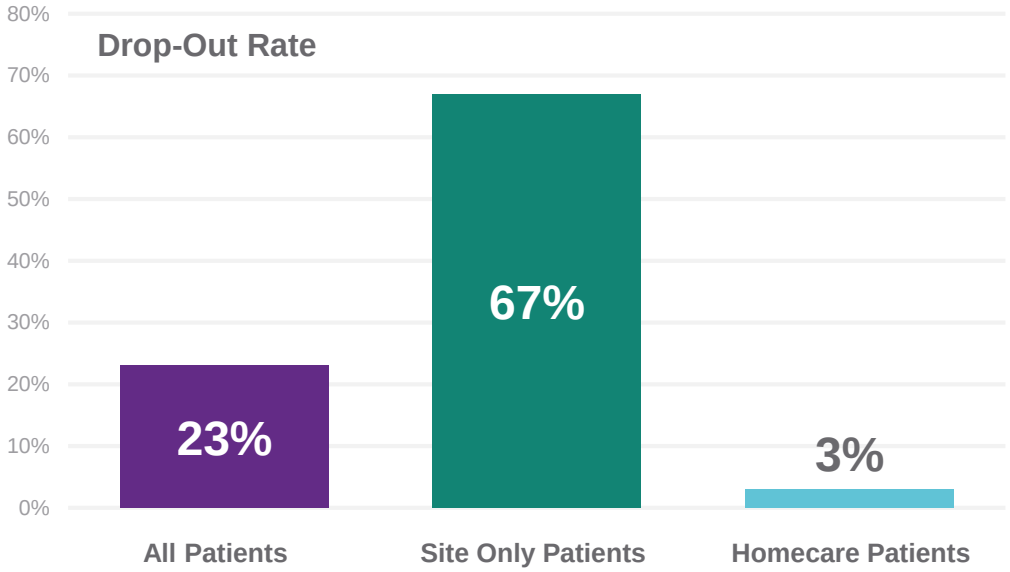
Services available **WEEKENDS AND EVENINGS**

Services available for **RETESTS AND TRAVELING PATIENTS**

Case Study In-Home Services – Enhanced Retention

Use of in-home clinical services vs. traditional site visits

N=529 Patients, 363 (69%) Used Homecare Services



Dramatic improvements recognized:

Subject
RETENTION INCREASED

ONLY 3%
of homecare patients dropped out

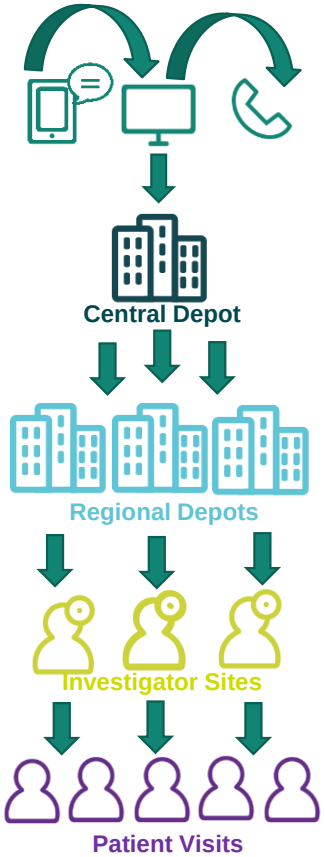
OVER 500 PATIENTS
enrolled

INCREASED COMPLIANCE
with blood draws

Kit & Supply Distribution

Direct to Patient distribution methods to ensure no interruptions, protect patient safety & comfort

Traditional Distribution Process



Direct To Patient Distribution
- Investigator site to patient
- Regional depot to patient
- Central depot to patient

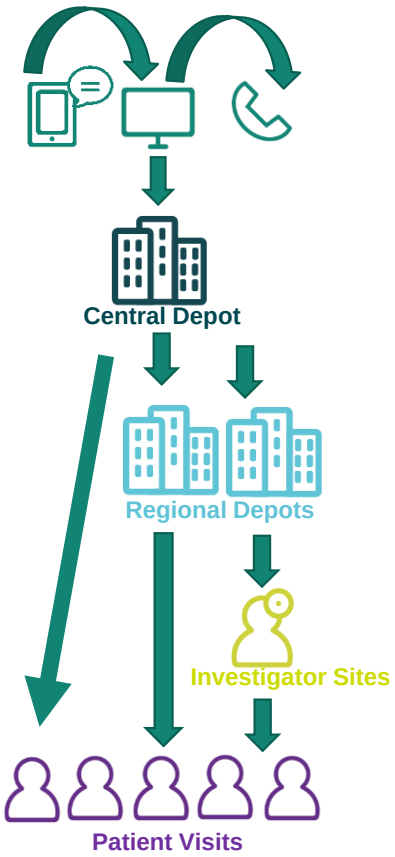
Supply chain effects - reduction of stock Levels

Drug supply distribution plan - set-up to accommodate different distribution options

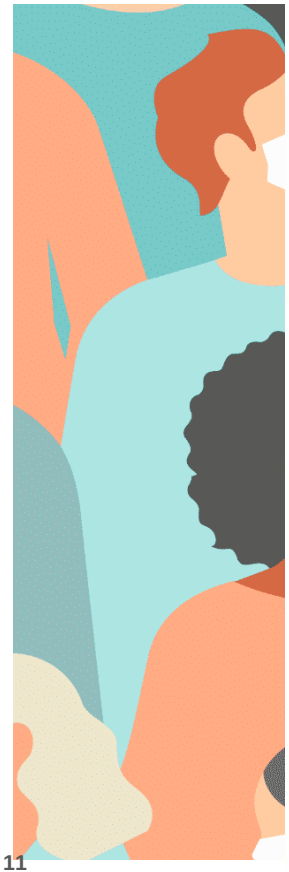
Patient supplies - will IP be stored at the patients home and any special requirements

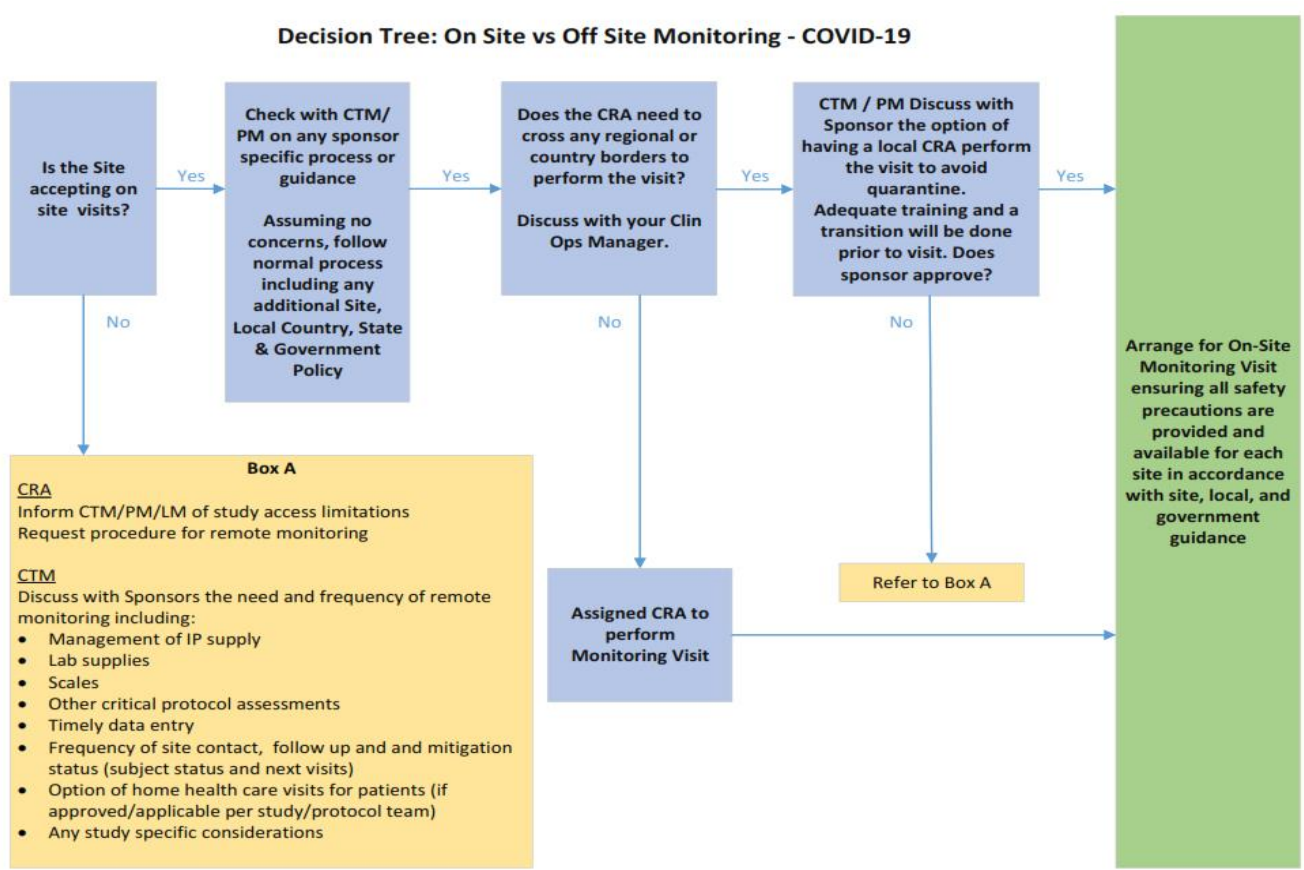
Integrations between IRT and drug distribution vendors is key

DTP Distribution Process



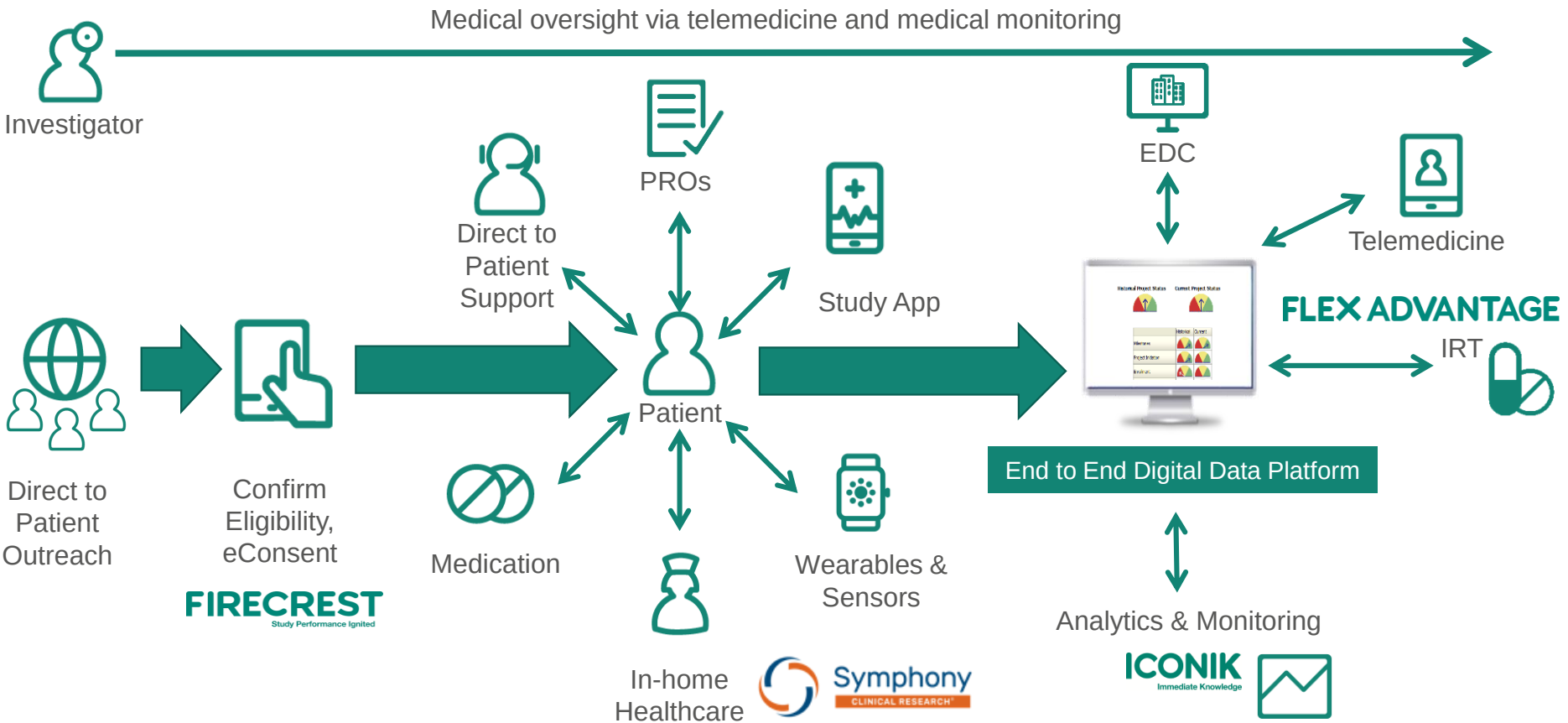
ICON Decision Tree to Optimize Site Monitoring





Decentralized and Hybrid Study Ecosystem

Leverage end to end digital platform to integrate systems, reduce data entry, provide real-time data access, patient engagement, monitoring & decision making to promote resiliency



Contracting / Budgeting

- Technology Contract/License Model
  - License options = Perpetual, SaaS, term or consumption based
  - Contract models = Enterprise (ELA), Pay as you go (PAYG), etc
- Monitoring and negotiation on project management (PM) and support fees
  - Reduced PM fee's year on year throughout life of project
  - Ensure PM & Support fees are consistent with the project requirements
- Discounts
  - Multiyear deals
  - Partnering to help develop new technologies
  - Prepay maintenance and support (long term)
- Equipment rental & purchase options analysis
  - Reclamation and disposition of equipment at study end.
- Focus on termination notice requirements (No auto - renews)

Compliance Management

- GxP Assessment
  - Will the technology or software be used to create, modify, maintain, archive, retrieve, sign/approve, or transmit records required by a health authority?
  - Will the technology or software be used to implement or enable quality management practices required by a health authority?
  - Will the technology or software be used in production or distribution of products regulated by a health authority?
  - Will the technology or software be used as a medical device or a component, part or accessory of a medical device, per health authority definitions of medical devices?

Compliance Management

- 21 CFR Part 11 Compliance
  - Does the application or system permanently store data that is utilized for any regulated activity?
  - Is the date required to be maintained under predicate rule requirements and is it maintained within the system in electronic format in place of paper format?
  - Is the data required to be maintained in electronic format in addition to paper format, and is the electronic format data relied on to perform regulated activities?
  - Is any of the data stored within the application or system submitted to regulatory agencies (even if such records are not specifically identified in the regulations?
  - Does the application or system employ electronic signature capabilities to provide the sole record of the signature on a document subject to review by a regulatory agency?

Clinical Trial Changes Relating to COVID-19

- **Over 60 countries have issued COVID-19 related Guidance impacting the conduct of clinical trials (current or future)**
  - Many of the larger CA have issued multiple COVID-19 related Guidance.
  - For instance, FDA has issued 52 COVID-19 specific Guidance. MHRA and EMA have similarly issued multiple Guidance in response to COVID-19.

- **These Guidance will ‘sunset’ with the expiration of the “Public Health Emergency”**
  - No information has been published by FDA, MHRA or EMA, outlining a timeline for reversion to normal operations. EMA has acknowledged the concern, but has issued no Guidance to specify what processes or timelines should be followed

FDA Guidance (summary)

Summary of the major recommendations follows:

- Multiple reference is made to proactively work with the site, investigators, EC/IRB and FDA regarding protocol changes
- Immediate changes to study procedures without EC/IRB or FDA consultation is allowed ‘to minimize or eliminate immediate hazards or protect the life and well-being of research participants’
  - ‘immediate hazards’ and ‘protect the life’ are very high standards to meet and document
- Documentation of reasons for contingency measures taken and impact assessment should be generated and maintained for future inspection
- Existing regulatory requirements for maintaining investigational product accountability remain intact and should be addressed and documented when utilising alternative distribution procedures
- Sponsors are directed as part of a future CSR to include analysis and reporting of the possible impact of COVID19 on the scientific integrity of the study
- **Remote or alternate treatment of patients is possible but requires risk assessment and documentation in study records**
  - **Specialized staff training, Pt acceptance and privacy, changed schedules, alternate methods of assessment, etc., should be considered**

Regulatory Acceptance of Novel Approaches for the future?

"…the FDA's recent guidance allowing researchers to make more modifications to study practices is a hopeful sign that regulators may be gaining more confidence in novel approaches. We may see a new normal once we put this pandemic behind us and move beyond very partitioned pilot activities to see broader use of different approaches."

Ken Getz, Deputy Director & Research Professor

Tufts University Center for the Study of Drug Development CenterWatch Monthly, May 2020

Innovations to Evolve Trials & Drive Predictable Delivery

What do Sponsor, Investigators and Patients need?

- Fewer countries, fewer sites = Reduced costs, decreased timelines for start-up, minimizes risk of disruption
- Recruit patients faster due to digital outreach and patient centric strategies = Reduced timelines for recruitment
- Reduced # on-site patient visits & frequency = Less patient and site burden
- Home based patient visits and DtP contact = Increased patient satisfaction, compliance, retention, more resilience
- Data integrations & centralization = real-time access & consistent visibility into data, opportunities for remote monitoring & RBM, trending and safety monitoring, less prone to disruptions
- Orchestration of strategic technology, workflows, data collection = more resilience, less prone to disruptions
- Overall reductions in duration of the trial = Faster results, faster decisions, less time to market, reduced cost

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