



DCT 4G Clinical

October, 2021

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Survey Reminders:

- Find surveys on the **GCSG App**.
- Tell us how the session was!
- Suggest topic ideas!
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CASE STUDY: USE & BENEFITS OF IRT FOR MANAGING COMPLEX ADAPTIVE STUDIES

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GCSG US VIRTUAL CONFERENCE – APRIL 26 – 29 2021



Workshop Description and Learning Objectives

Clinical study design is evolving as we work to accommodate flexibility in protocol deliverables and execution. This session will discuss how design has a critical role for adaptive multi-product trials.

Learning Objectives:

- (1) Define what basket studies are and how they are used in clinical trials
- (2) Discuss regulatory nuances specific to basket studies
- (3) Describe at least two (2) options for maintaining supplies for adaptive trials



Poll 1: Is your company conducting adaptive trials?

- ☐ YES (BioPharma Sponsor Company)
- ☐ NO (BioPharma Sponsor Company)
- ☐ DON'T KNOW (BioPharma Sponsor Company)

- ☐ YES (Vendor Company)
- ☐ NO (Vendor Company)
- ☐ DON'T KNOW (Vendor Company)



What are Adaptive Trials??



Adaptive Designs – The Definition

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”

(FDA “Adaptive Designs for Clinical Trials of Drugs and Biologics - A Guidance for Industry Nov-2019)

More EFFICIENT, More INFORMATIVE, More ETHICAL



Adaptive Designs – Concepts & Advantages

Important concepts:

- Interim Analysis
- Comparative vs Non-comparative analysis (Unblinded vs Blinded)
- “Prospective” == defined in protocol (prescribed schedule)
 - Number and timing of interim analysis
 - Type of adaptation
 - Statistical inferential method
 - Specific algorithm governing adaptation decisions

Advantages:

- Respond to information that was not know prior to trial start
- More quickly identify drugs (or devices) that have a therapeutic effect and to zero in on patient populations for whom the drug (device) is appropriate



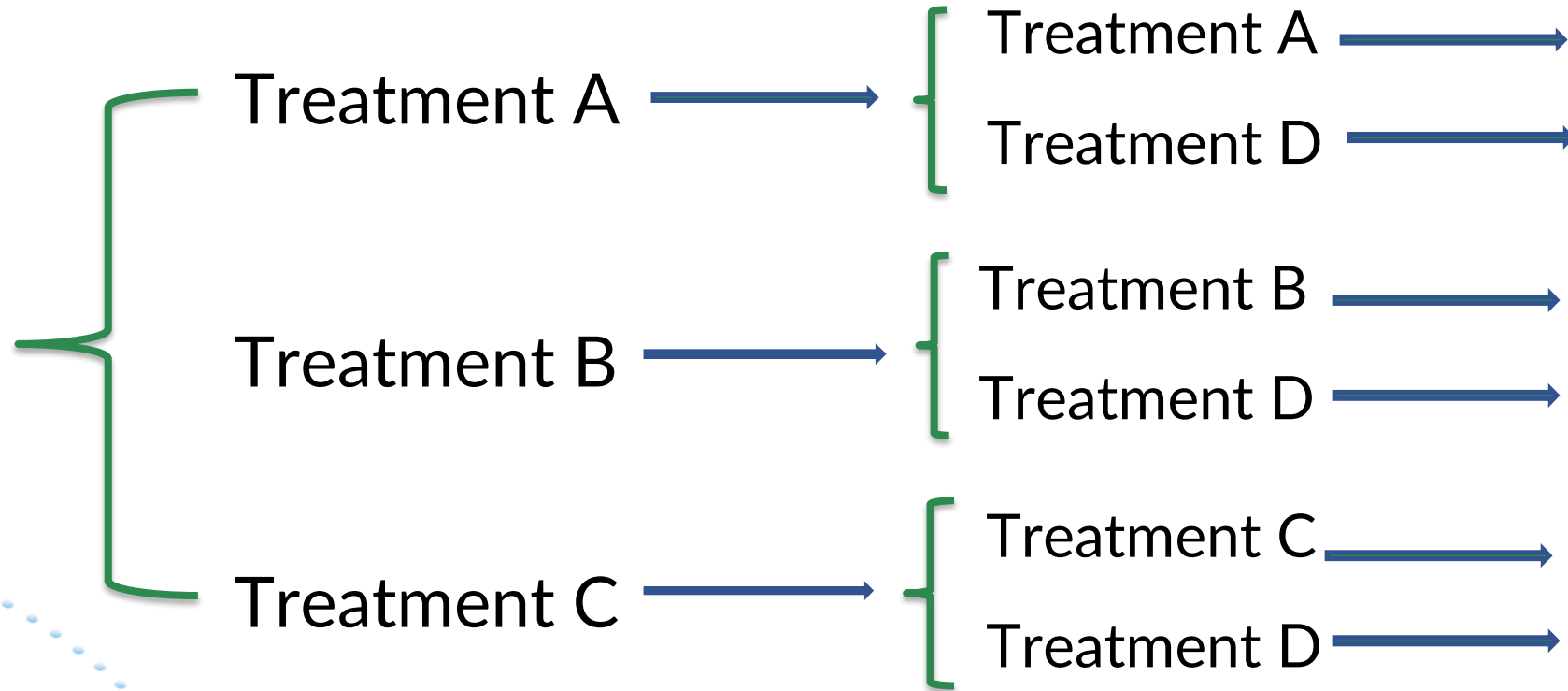
Adaptive Designs –Types_(non-exclusive)

- Group sequential design – early ending based on collected data
- Adaptations to sample size – respond to know variance vs assumed variance
- Adaptations to patient population – targeting to most responsive population
- Adaptations to treatment arm selection – adding/terminating arms, dose ranging
- Adaptations to patient allocation – balancing treatment groups (minimization) or varying treatment group assignments over course of trial
- Adaptations to endpoint selection – switch between acceptable primary endpoints
- Adaptations to multiple design features – combining 2 or more of the above



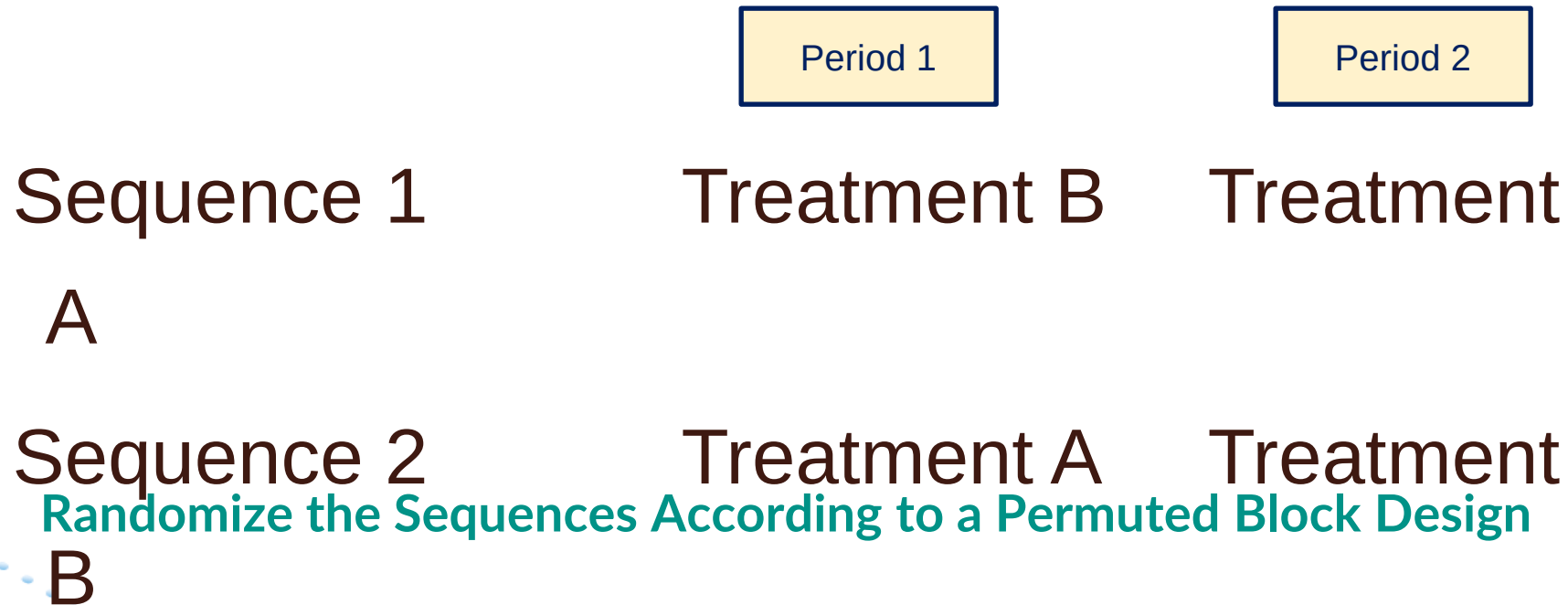
Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

1. Parallel, Double Randomized



Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

2. Crossover

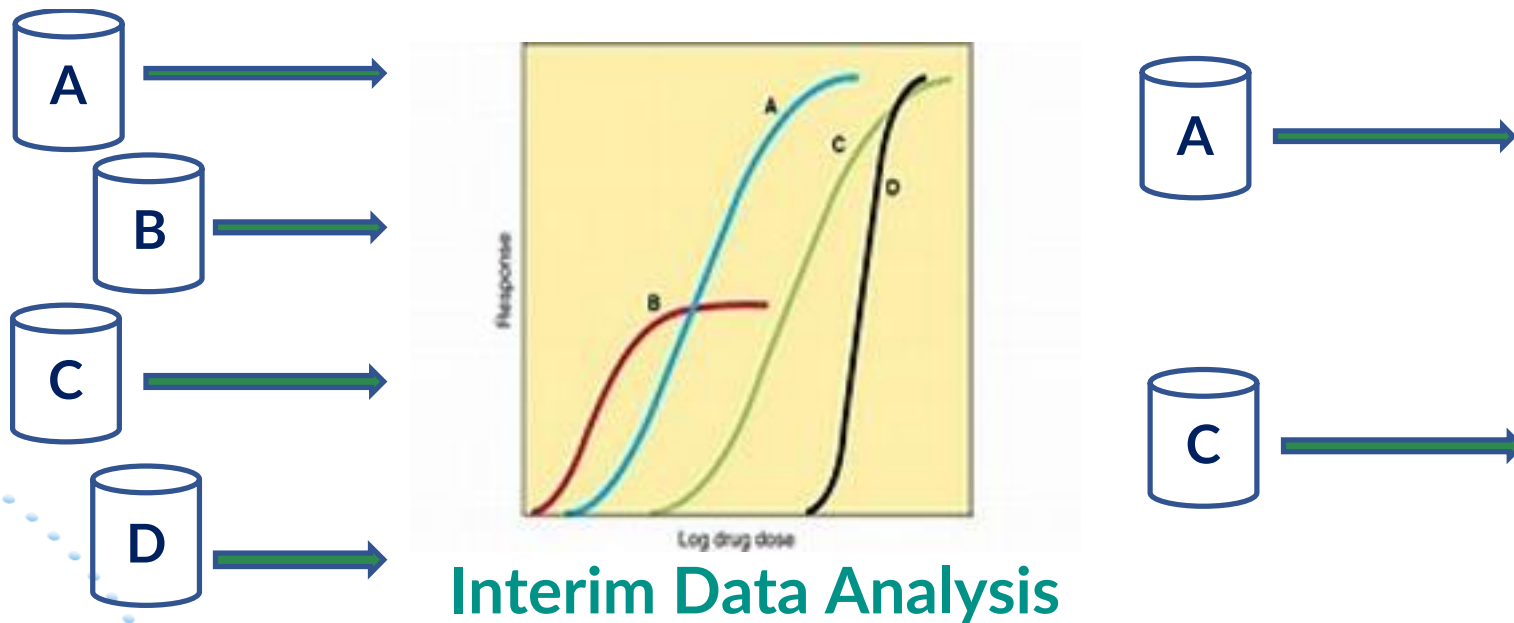


Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

3. Prospective Adaptive

Protocol is written to adapt to information obtained from interim data during the trial

Adaptive Dosing - remove dosing arms based on toxicity or efficacy



Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

4. Cohorts

Determination of optimal doses and expansion based on recommended dose.

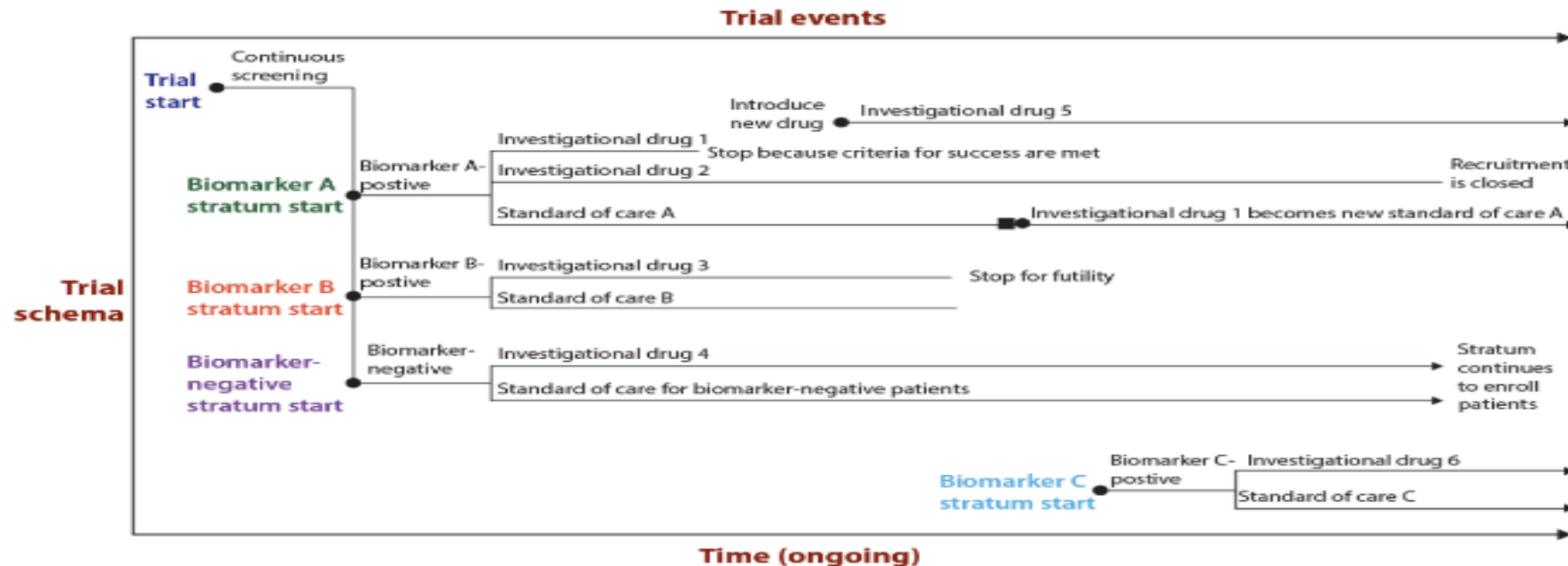


As dose levels are approved and the escalation progresses, subjects in the lower-dose cohorts may be titrated up to the most recent dose level approved.

Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

5. Platform Trials

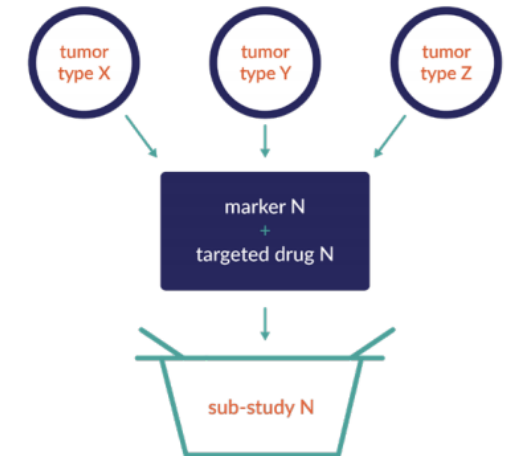
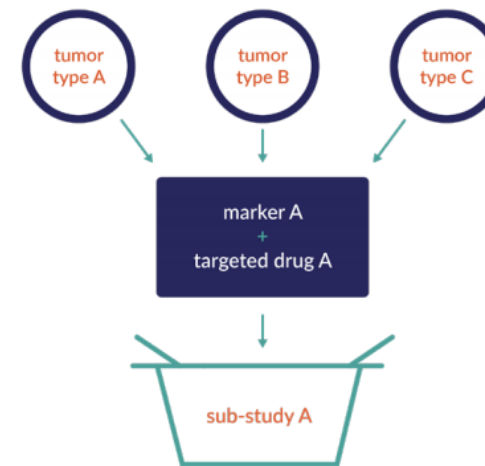
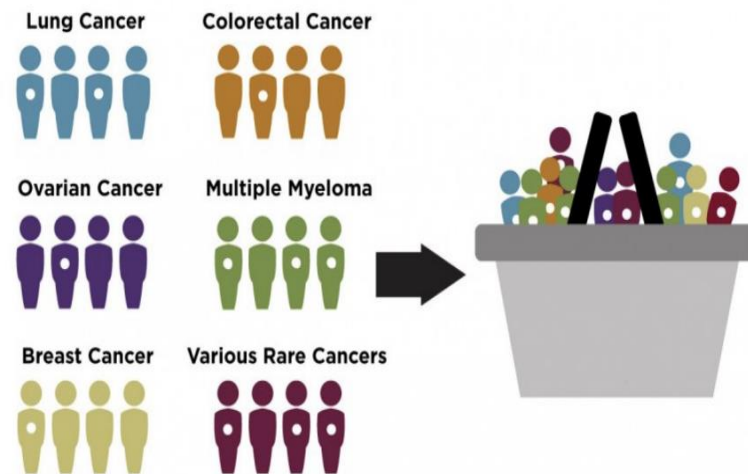
Study multiple, targeted therapies for a single disease more or less perpetually, with treatments allowed to drop in or out of the platform depending on how well they perform in the trial



Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

6. Basket Trials

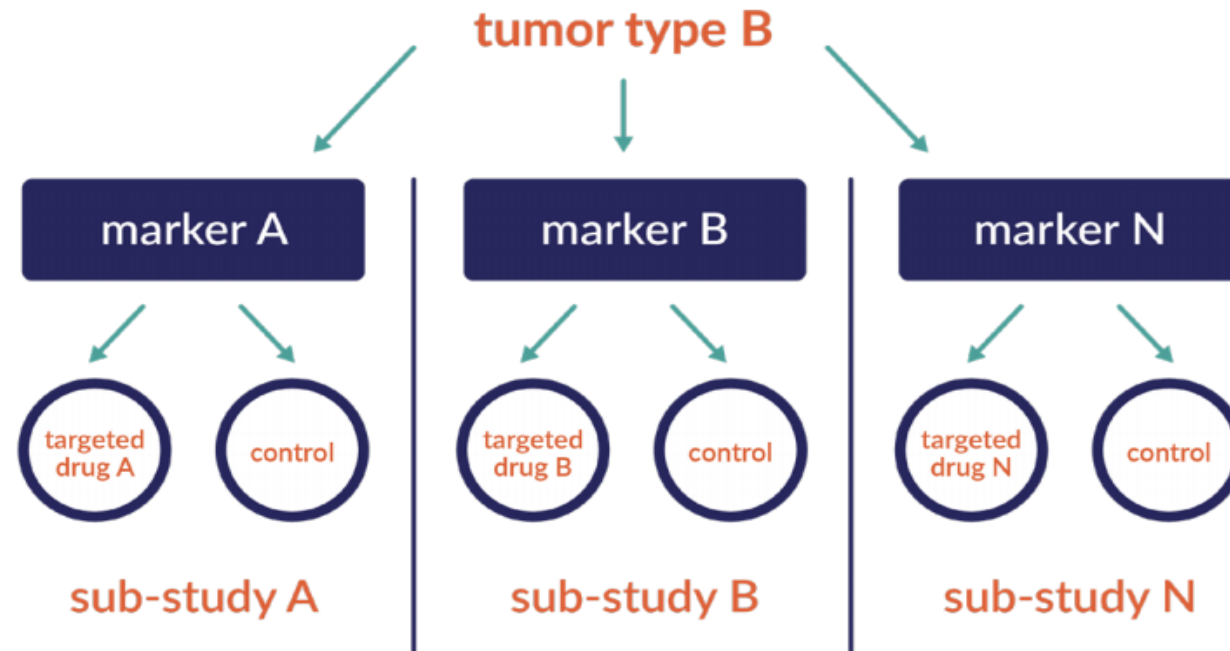
Basket trials test the effect of **one drug** on a single mutation in a **variety of diseases** (ie. tumor types), at the same time.



Adaptive Design Examples (From GCSG RTSM/IRT Bootcamp)

7. Umbrella Trials

Umbrella trials study **several therapies** for a **single disease** but focus on various subgroups (usually determined by biomarkers) of a disease



Poll 2 – What types of adaptive trials does your company conduct? Choose all that apply:

- | | |
|--|--|
| ☐ Dose Escalation Phase I | Find maximum tolerable dose (MTD) |
| ☐ Seamless Phase I/II | Combine safety and activity assessment in one trial |
| ☐ Seamless Phase II/III | Combine selection and confirmatory stages into one trial |
| ☐ Adaptive Dose Ranging | Shift allocation ratio towards more promising/informative dose(s) |
| ☐ Adaptive randomization | Shift allocation ratio towards more promising/informative treatment(s) |
| ☐ Platform Trials | Single disease, multiple therapies varying upon interim analysis |
| ☐ Basket Trials | Variety of diseases, single treatment |
| ☐ Umbrella Trials | Single disease, several therapies |
| ☐ Group Sequential | Number of patients is changing based on group analysis |
| ☐ Multi-arm Multi-stage | Multiple treatments, doses, durations or combinations with option to stop and/or select best |

Case Study

Phase 1/2 Oncology Adaptive Trial and its RTSM(IRT) Journey



Case Study: Phase 1/2 Oncology Adaptive Trial and the RTSM(IRT) Journey

- Study Description

A **Phase 1/2**, First-in-Human, Open-label, **Dose Escalation Study** of CCC2021 (TRIPLEC2021) Monotherapy and in Combination with Pembrolizumab in Patients with Solid Tumors. Followed by **Basket Expansion** of CCC2021 in Combination with Pembrolizumab in Patients with Specified Solid Tumors



Case Study: Phase 1/2 Oncology Adaptive Trial and the RTSM(IRT) Journey (continued)

- Study Objectives
 - Phase 1 Dose Escalation: To determine recommended phase 2 dose, safety, and assess PK
 - Phase 2 Basket Expansion: To assess efficacy
- Package Types
 - CCC2021: 50 mg 30ct bottle, 100 mg 30ct bottle & 90ct bottle, and 400 mg 30ct bottle
 - Pembro: Kit



Case Study: Phase 1/2 Oncology Adaptive Trial and the RTSM(IRT) Journey (continued)

- Number of Patients
 - Phase 1 Total: 88 patients
 - Dose Escalation Cohorts: Up to 48 patients
 - Expansion Cohort: Up to 40 patients
 - Phase 2 Total: 60 patients
 - Basket Expansion – Gastric Cohort: 25 patients
 - Basket Expansion – Colorectal Cohort: 20 patients
 - Basket Expansion – Pancreatic Cohort: 15 patients
- Study Total: Allows up to 148 patients

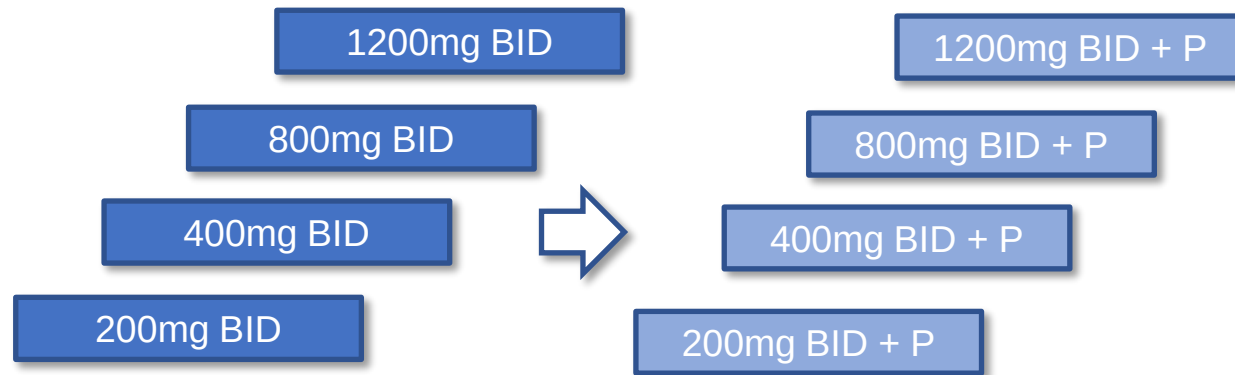


Case Study Schema

Ph1a: CCC2021 Dose-Escalation

Ph1b: CCC2021 + Pembro(P)

Ph1b: Expansion Cohort



Multiple Tumor Types
(Cohorts of 3 – 6)

RP2D CCC2021 + P

Protocol Amendment:
Expansion cohort added to
ph1. N = up to 40 pts

Ph2: Basket Expansion Cohorts

Gastric
Pembro + CCC2021
N = 25

Colorectal
Pembro + CCC2021
N = 20

Pancreatic
Pembro + CCC2021
N = 15

Case Study Developments

- Multiple protocol revisions to refine study design as study progressed
 - Added cohort to phase 1 to further evaluate dose response before initiating phase 2
 - Phase 1 timelines extended
- Tablet strength modifications to improve drug activity
- Bottle tablet count increased to minimize site and depot inventory and number of bottles dispensed per cycle



Case Study Hurdles and the Use of Technology

Case Study Hurdles & Improvements	Use & Benefits of Technology
Intra-subject dose escalation	Configurable system, system alerts, dose escalation and dispensation features
Pembro added to subjects on monotherapy	Flexible cohort management, change dispensing features, approval functionality
Dose level drug strength modifications	Dispensing logic functionality, alternate/flexible dispensing options for rapid response
Additional titration levels built in	Multiple level titration table
Bottle table count modifications	Build to match, robust supply management, flexible inventory settings
Additional phase 1 cohort added	Real-time system updates, fast builds, protocol versioning



Poll 3: What technology capabilities are most important to your company?

- ☐ Configurable System (build to match, multi-level titration table)
- ☐ Speed (fast builds)
- ☐ System Alerts (real-time system updates)
- ☐ Supply Chain Management (flexible inventory management, multiple kit types)
- ☐ Approval Functionality (protocol versioning, lot release)
- ☐ Control of Changes (cohort management, dispensing features)
- ☐ All of the above



Case Study: Advantages

- Advantages of the adaptive trial design
 - On-going data analysis and protocol amendments to target tumor types with positive response.
 - Fewer patients needed to determine optimal dose.
 - Flexible approach allowed on-going drug modifications without stopping the train.



Case Study: Disadvantages

- Disadvantages of the adaptive trial design
 - Longer design phase to ensure effective outcome.
 - Complex study design (RTSM) management.
 - Real time changes required.
 - Greater level of communication and coordination required between everyone involved.



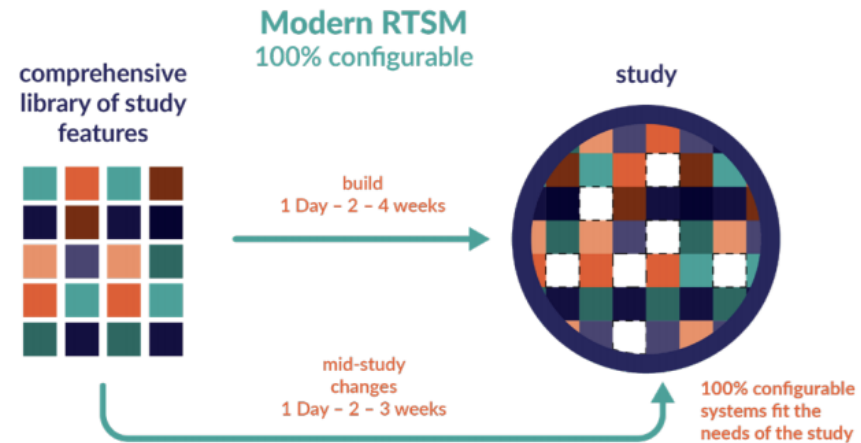
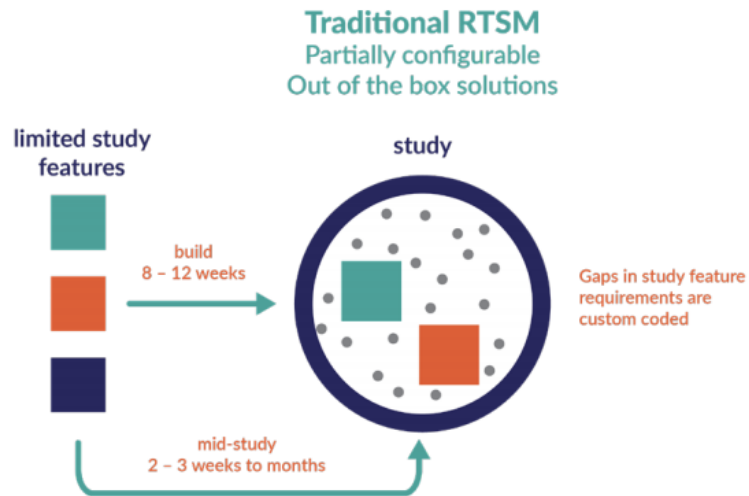
How IRT Systems Enable Adaptive Trial Designs



Adaptive Trials – RTSM Considerations

- Pro-actively prepare for change – Configure RTSM to any possible scenario that seems realistic
- “Demand” control on adaptive changes – Make yourself independent from the RTSM vendor

Traditional vs. Modern RTSM



RTSM Considerations for Adaptive Trial



Regulatory References:

FDA – Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, November 2019: <https://www.fda.gov/media/78495/download>

EMA – Adaptive pathways:

<https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways>

EMA – cGuidance for companies considering the adaptive pathways approach

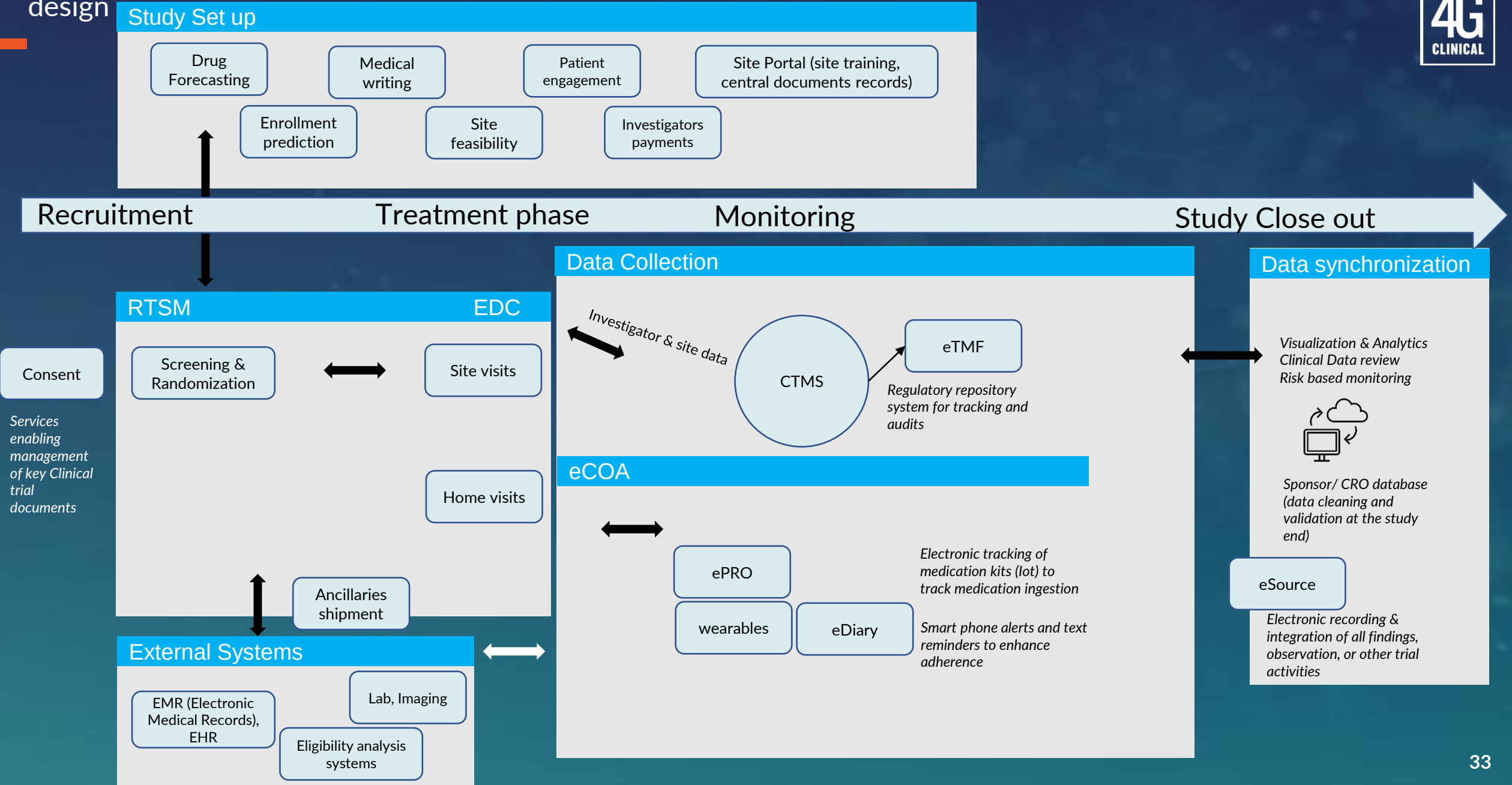
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-companies-considering-adaptive-pathways-approach_en.pdf



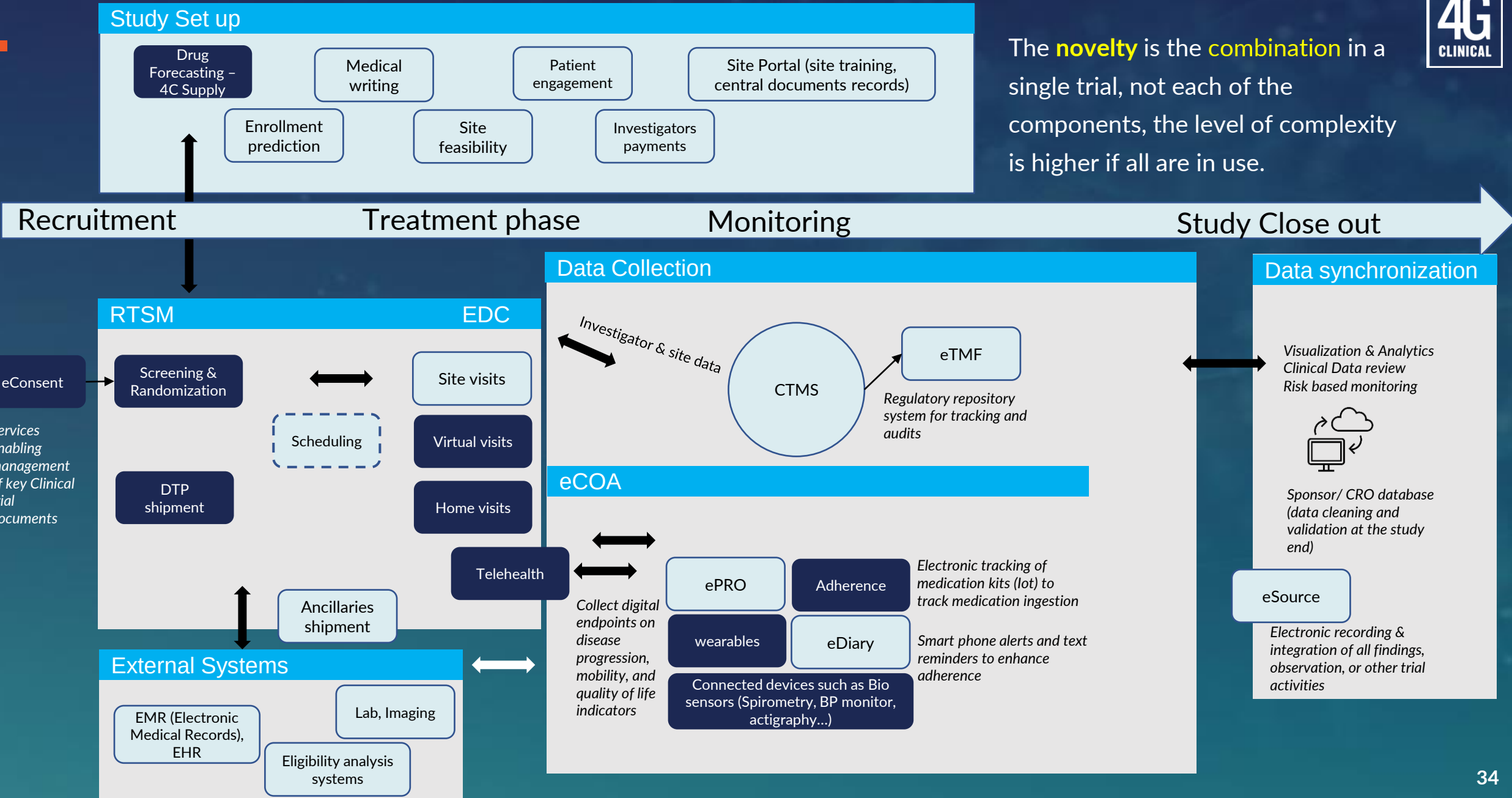
Talking points

- What is different in DCT from traditional study designs?
- Technology solutions required in a full DCT design
- What is the trend towards DCT? Any obstacles industry need to overcome before a real move towards DCT?
- Who are key vendors and what do we know about them?
- What DCT solutions does 4G has and what is WIP?
- What opportunities for 4G to a) build, 2) partner, 3) acquire?

Traditional trial technology design



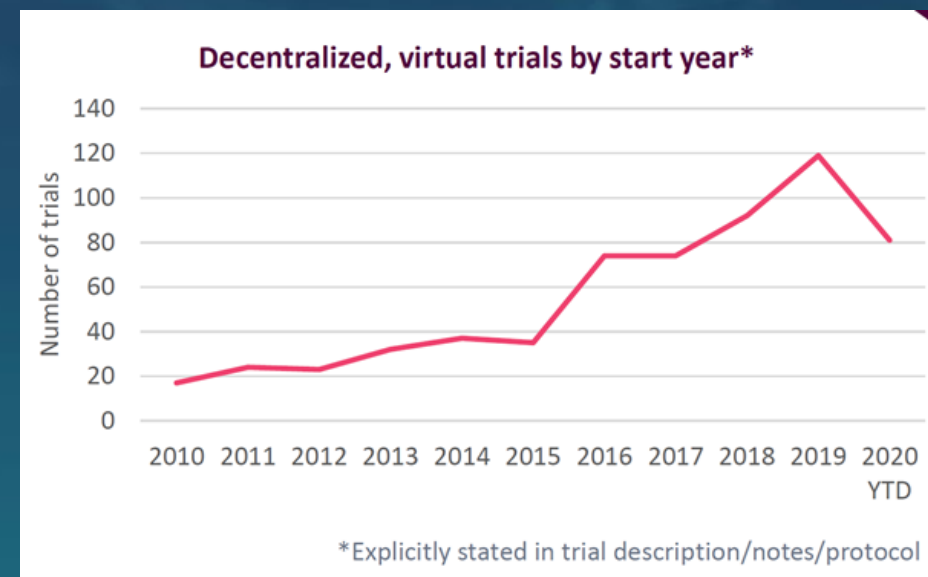
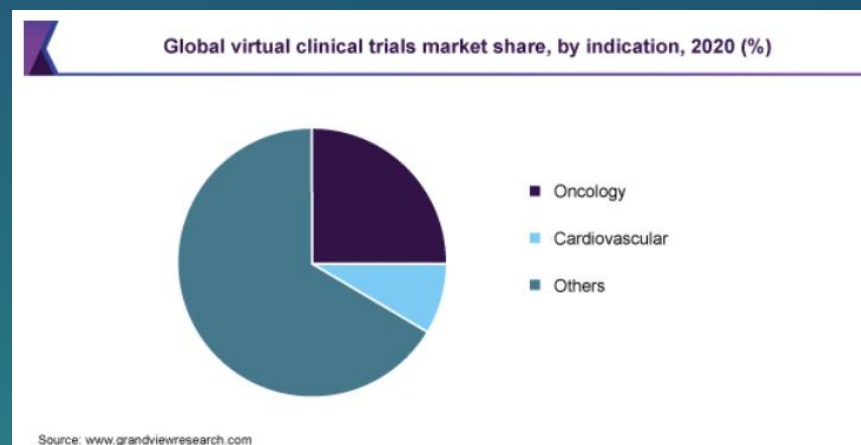
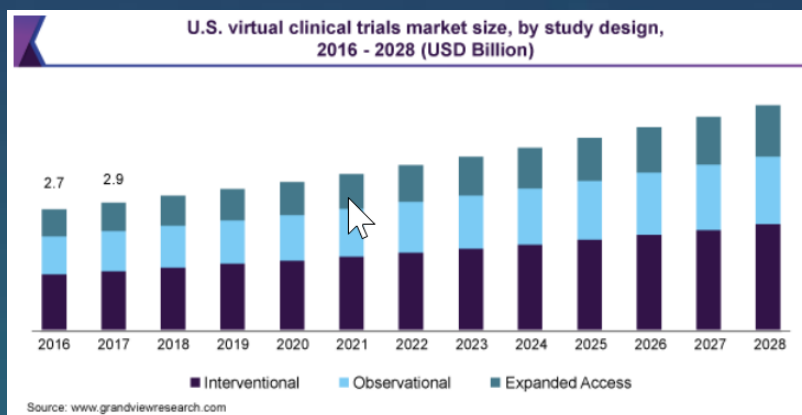
The **novelty** is the **combination** in a single trial, not each of the components, the level of complexity is higher if all are in use.



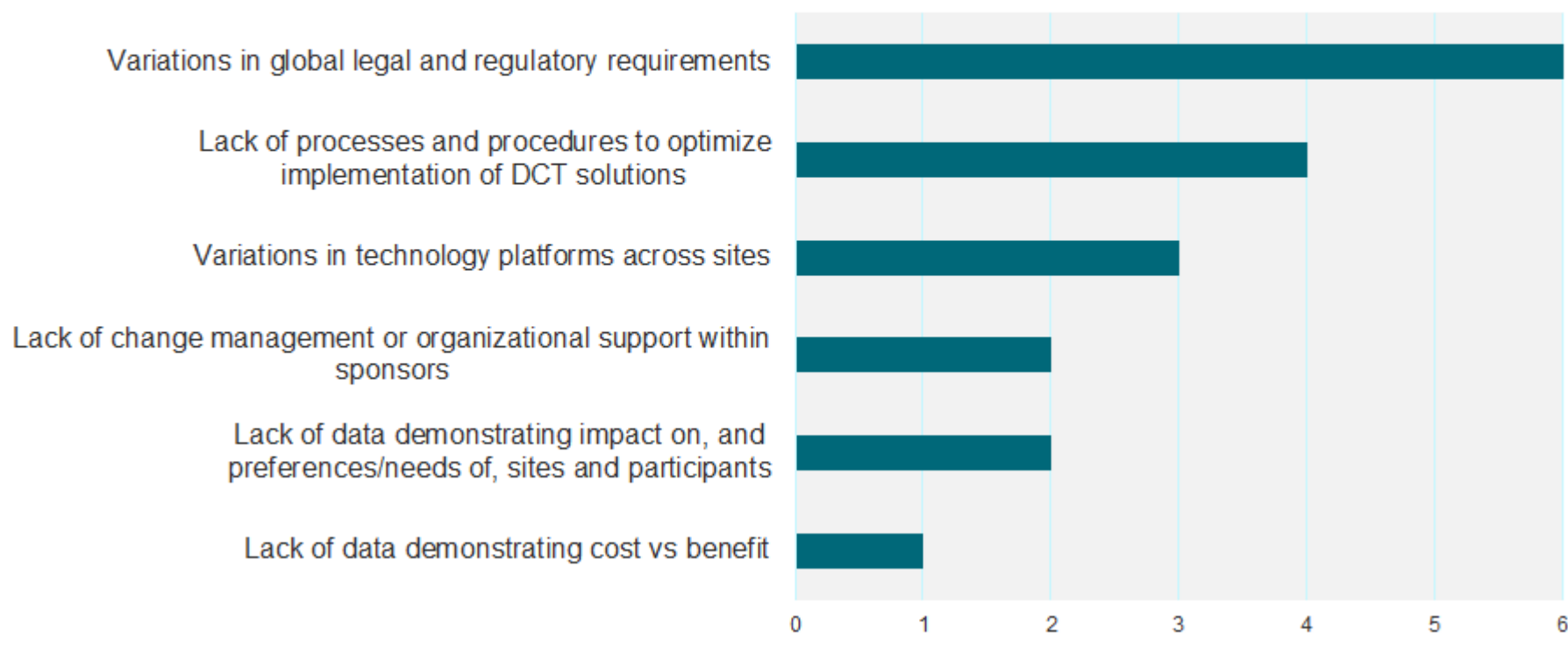
Trends in DCT

The global virtual/decentralized clinical trials market size was estimated at USD 7.4 billion in 2020 and is expected to reach USD 7.8 billion in 2021.

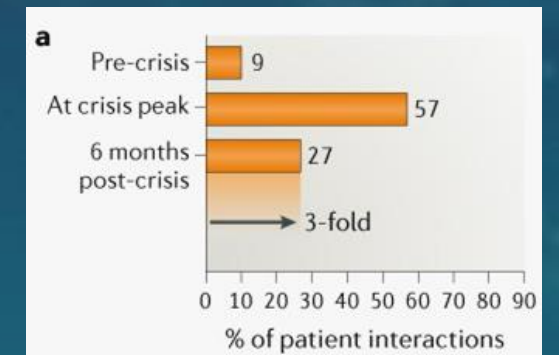
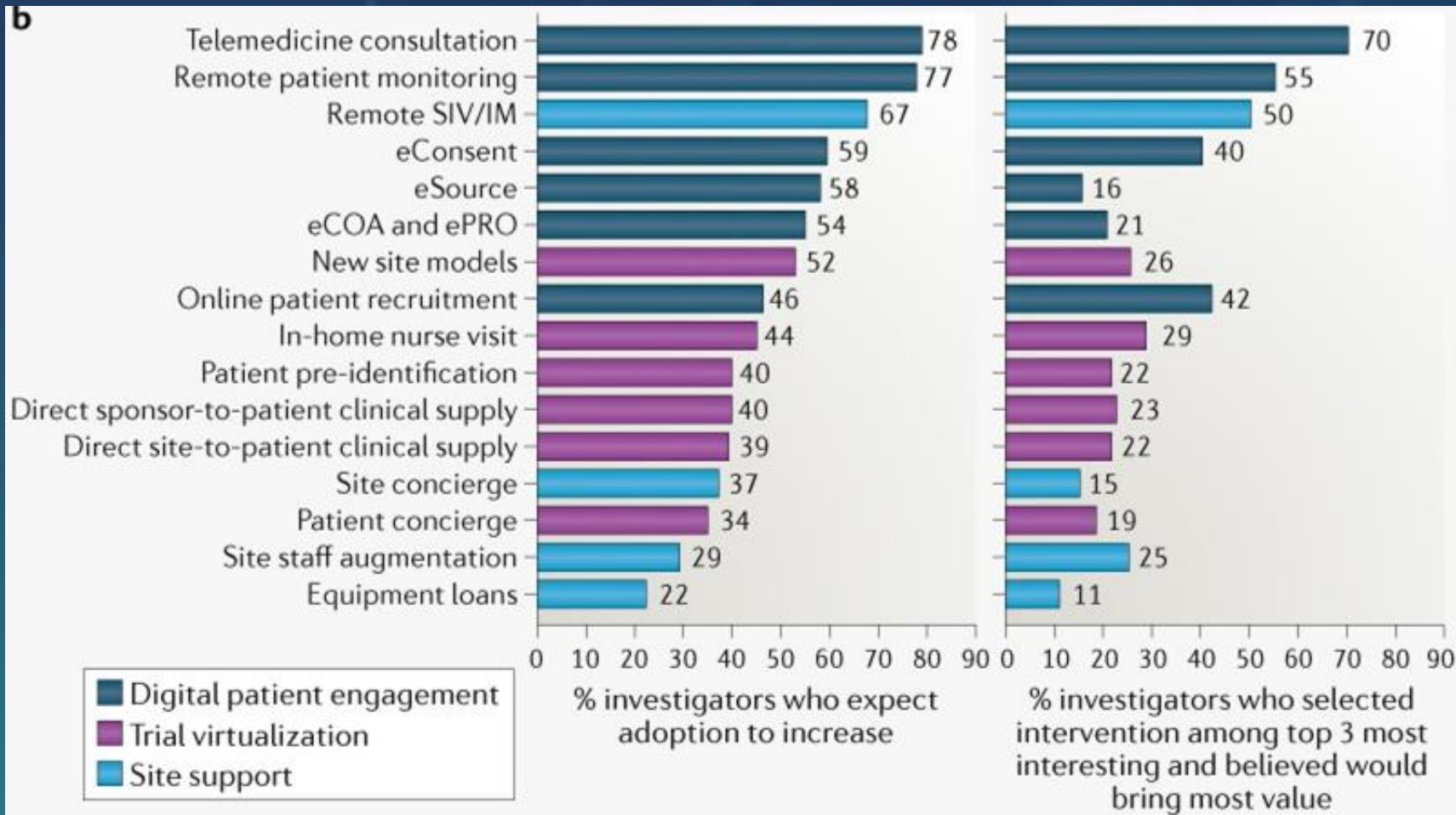
The global virtual/decentralized clinical trials market is expected to grow at a compound annual growth rate of 5.7% from 2021 to 2028 to reach USD 11.5 billion by 2028.



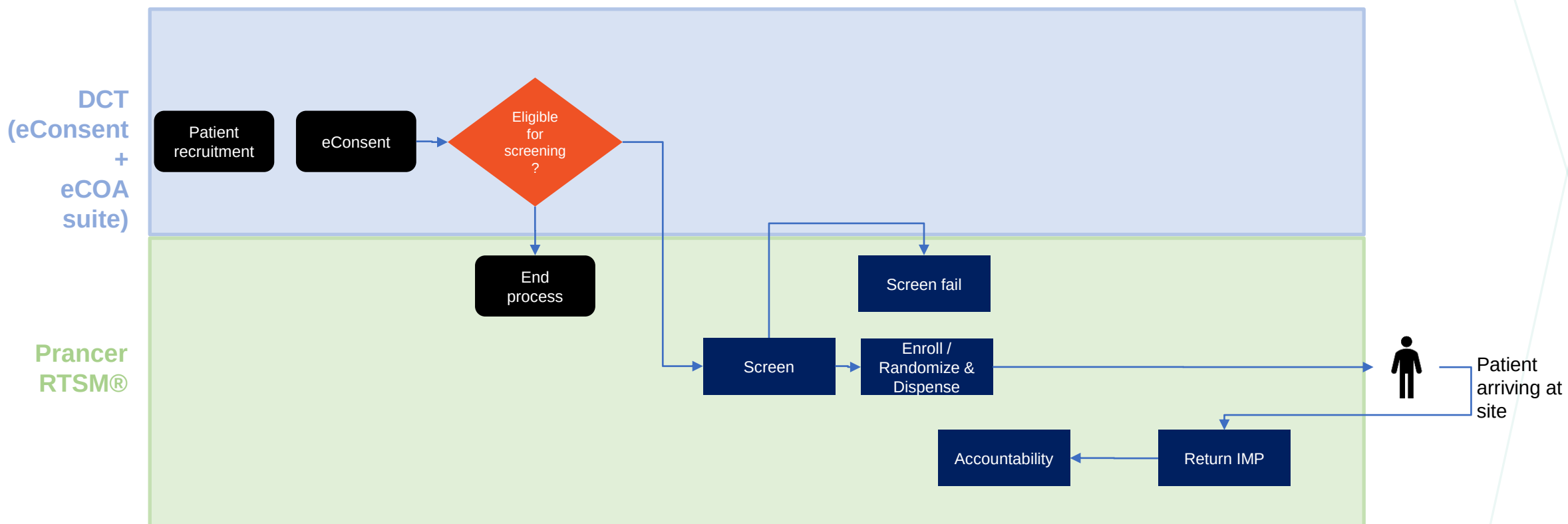
Which of the following do you see as the single greatest barrier to widespread adoption of DCT solutions in clinical trials?



CTTI: slide taken from the CTTI DCT expert meeting (Aug. 25/26, 2021)
<https://ctti-clinicaltrials.org/centralized-clinical-trials-expert-meeting/>



Traditional IRT set up for a clinical trial



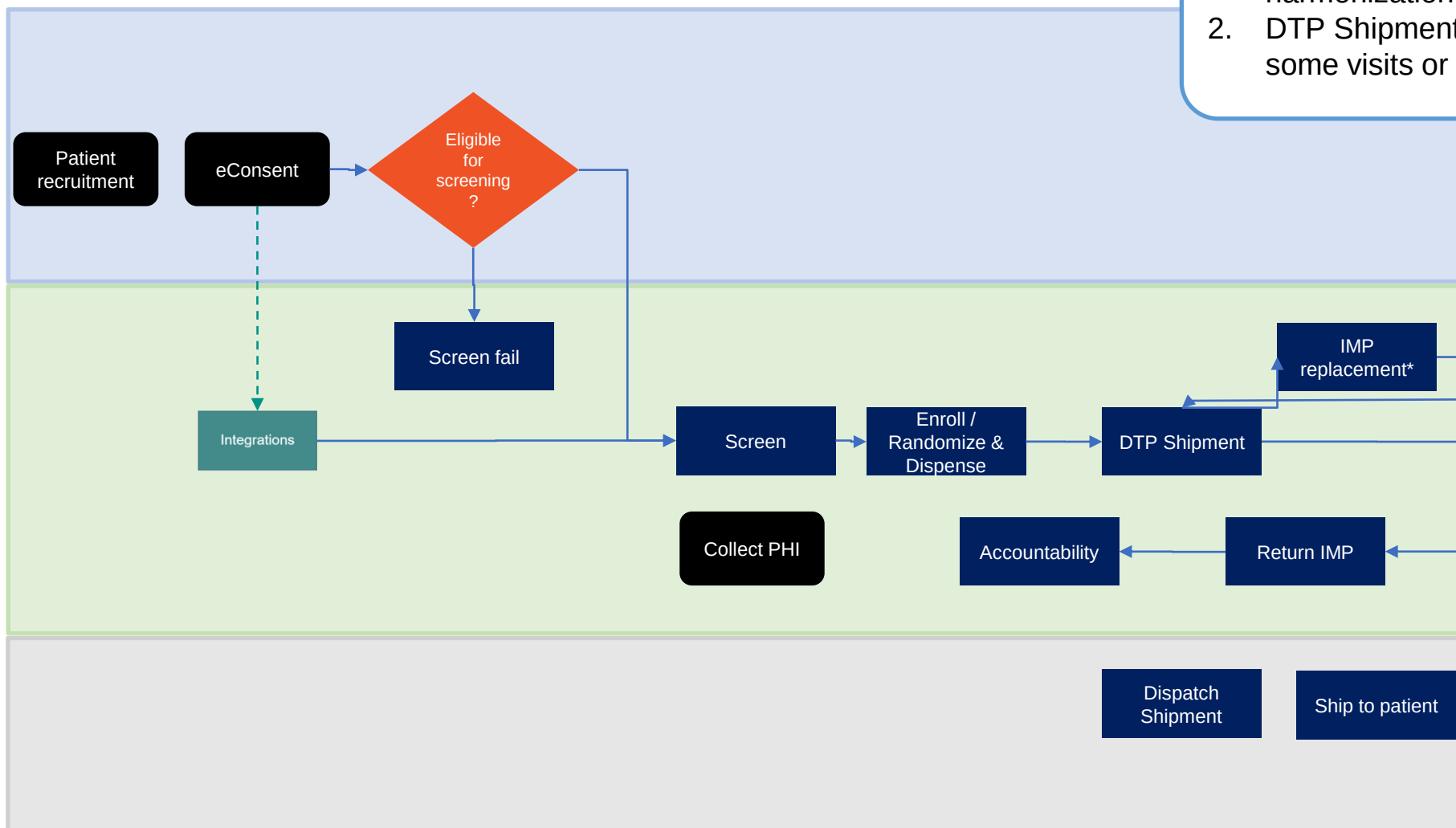
Option A – Lean DCT model

1. eConsent integration for patient ID harmonization
2. DTP Shipments to patient home for some visits or all visits

DCT
(eConsent +
eCOA
suite)

Prancer
RTSM®

LSP/Courier

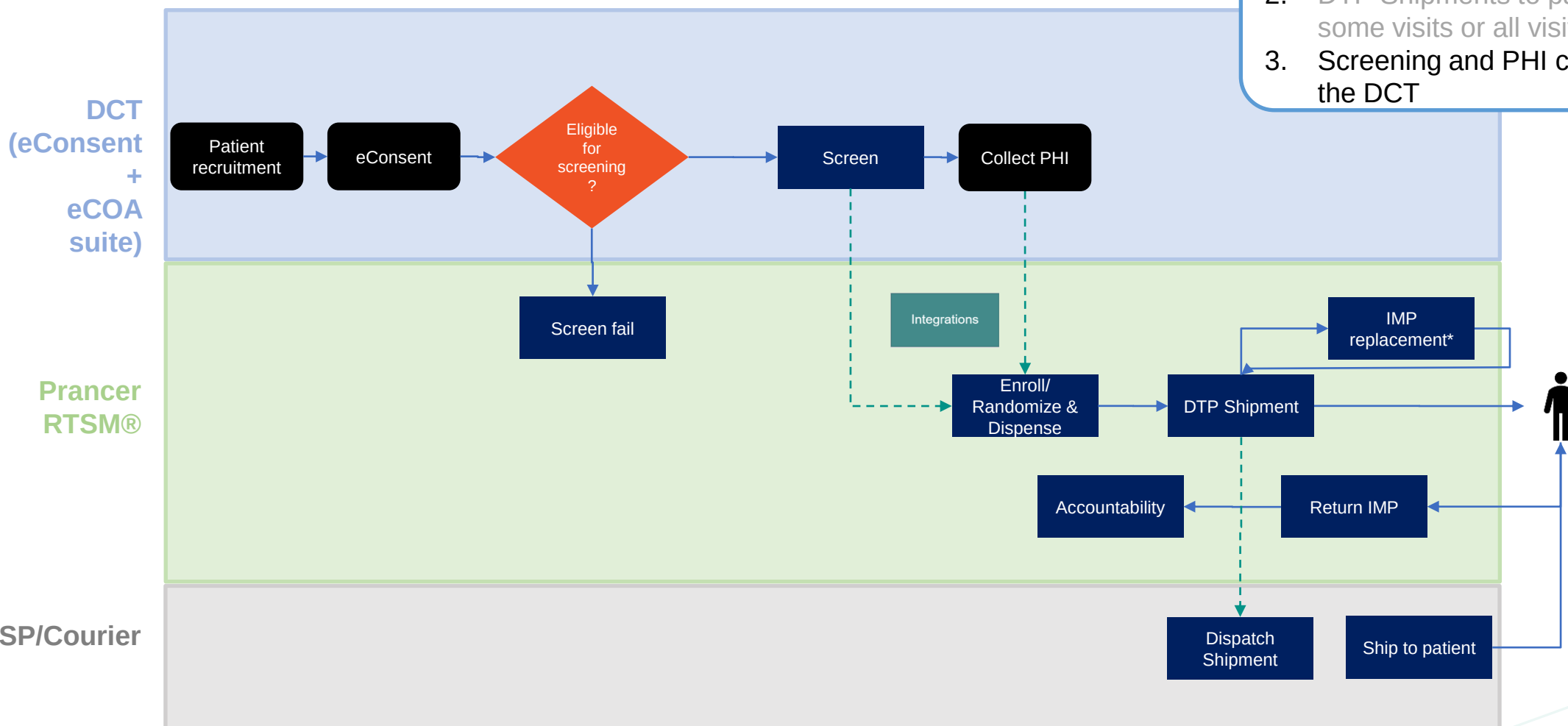


*In case shipment arrived as damaged/ temperature excursion or cancellation – IMP replacement is required

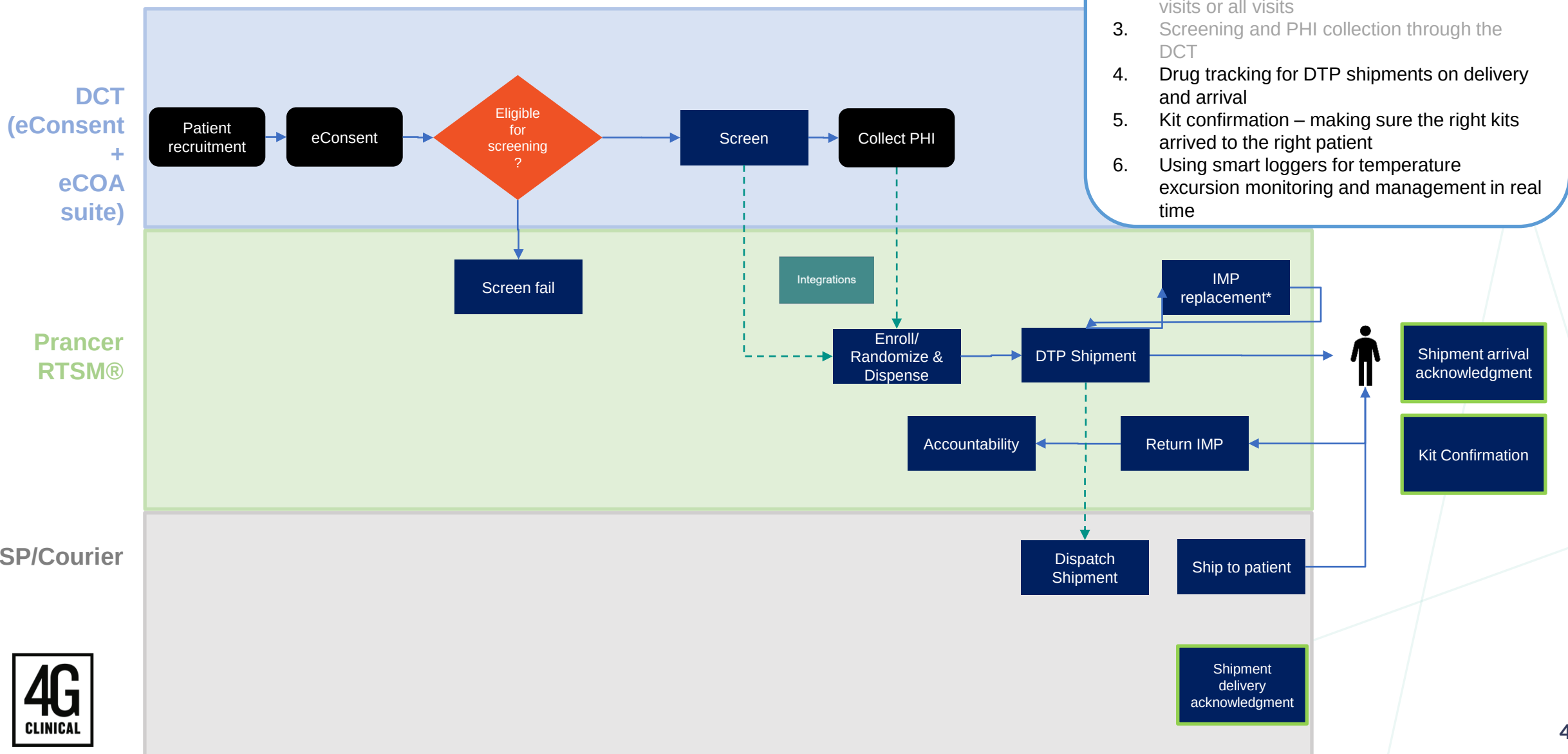


Option B – Advanced DCT integrations

1. eConsent integration for patient ID harmonization
2. DTP Shipments to patient home for some visits or all visits
3. Screening and PHI collection through the DCT



Option C – Advanced DCT integrations with Drug tracking (future)



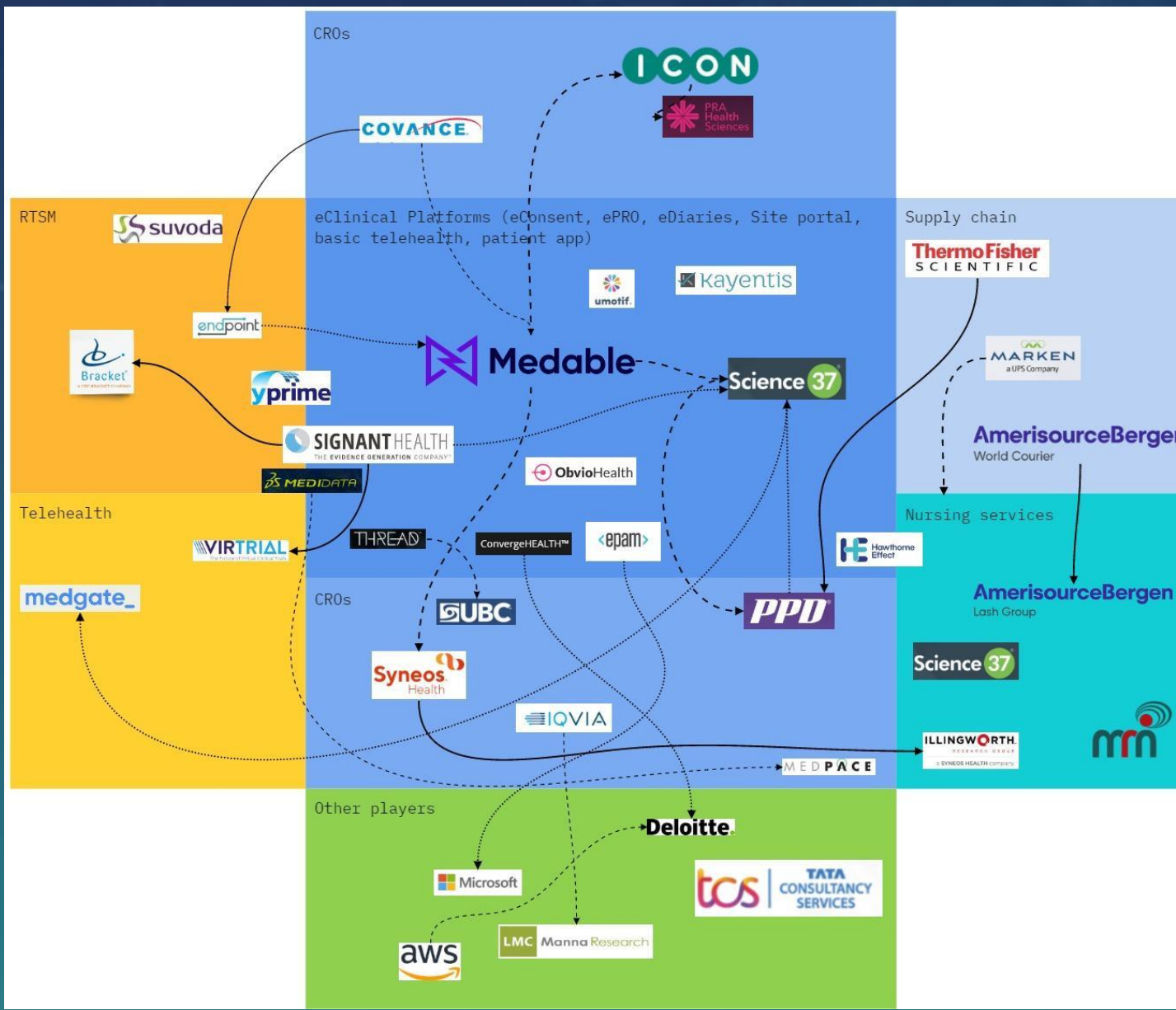
What can we offer for DCT today / WIP

- Patient ID harmonization between platforms
- DTP shipment:
 - Depot integrations
 - DTP shipment status tracking
 - DTP shipment auto receipt
- DfP – Pick up from patient - in the pipeline
- Kit confirmation at the patient home
- Kit accountability at the patient home
- Compliance / Adherence
- Reduce data entry (PHI, Patient ID)
- Drug Tracking to patient home & storage (PX)

DCT Future and 4G Opportunities

Opportunity
Build
Partner
Acquire

	NOW	FUTURE
Shipments	DTP sent to patient home from depot or site Taking pictures of kits in some cases	Shipment tracking (status) partner with couriers Sent to patient/ Point of care (anywhere) Kit level confirmation per shipment (right kit to the right patient concept) with barcodes - build integration to support
Drug Adherence	Black box eCOA solution sometimes used to track, not linked to IRT	Continuous monitoring - Smart Packaging Link IRT to eCOA to match data Enhanced Reporting
Temperature Monitoring	Until reached patient home	Drug tracking until arrived / At the patient home (Paxafe / DHL / real time trackers)
Patient Experience & Coordination	Phone calls, messaging, reminders, app notifications	Scheduling tools to scale up, apps notifications, drug reminders Shipment receipt
Drug Storage	Sent to patient per dispensing	Storage tracking at home
Accountability	Owned by sites, managed by sites	Owned by sites, managed by LSP, centralized

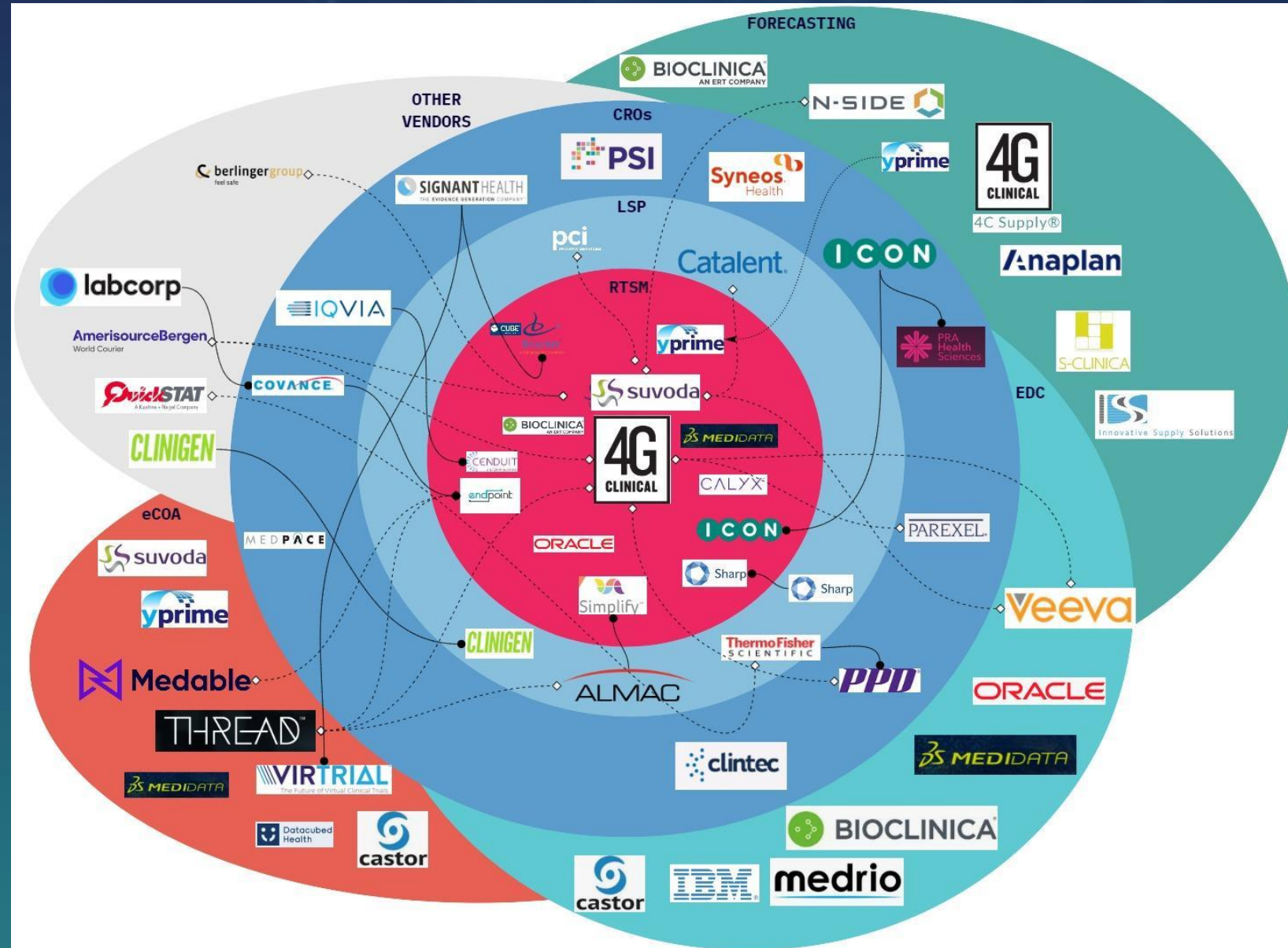


Key players

Medable (Full platform solutions)– 100 studies a year, investments estimated \$217M by GSR Ventures, PPD, Streamlined Ventures, National Cancer Institute, Sapphire Ventures and Obvious Ventures. Strong partnership with **Covance** (50 studies a year) and LabCorp. Strongly positioned as the market dominant in the DCT area.

Thread (Integrators)– 100 studies total since founded, investors Water Street and JLL Partners acquired the company in August 2019, and invested 50M in Aug-2020. Positioned as innovative service provider to enable DCT. Positioning strategy with a high number of industry partners such as: Trialbee (patient recruitment), 1nHealth (patient recruitment), Lokavant (data driven products like benchmarks, insights, predictions), MRN (nursing services), Advarra (IRB reviews). THREAD is currently supporting aprox. 50 -75 studies/ year, with the average TCV of a about \$750K. THREAD's PE backers are well known (and respected) in the HC/LS space.

Some other key players operating in the virtual/decentralized clinical trials market include Icon, Science 37, IQVIA, Clinical Ink, Parexel, and Covance.



Best in class strategy

2 models exist today:

1. Unified systems - all components under the same vendor
2. Integrators - plug and play each component. Integrate with existing systems used by a sponsor and add relevant components to the model chosen. This may require partnerships with different solutions and pre-built integrations to allow the data flow.

Paul, JNJ stated: unified systems are not a solution for a company as JNJ.
We look at the best RTSM, eCOA, EDC, etc and make them work well.

*DCT trials may best suit larger trials (more sites, more patients) - to boost enrollment and have a diversified population.



Thank You

Contact Information: