COVID-19對於臨床試驗執行實務之影響

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Outline

- Global Trend & Observations
- Feasibility Survey to Site Ready
- Ongoing Phase
  - Subject Enrolment
  - Monitoring
- Quality Control
  - Oversight process
  - Audit/ Inspection
- Recommendations

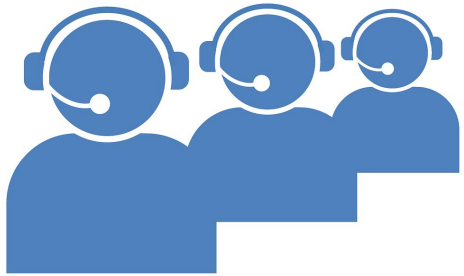
Global Trend & Observations under COVID

The desire for a consistent approach in an inconsistent environment

Changes under COVID-19

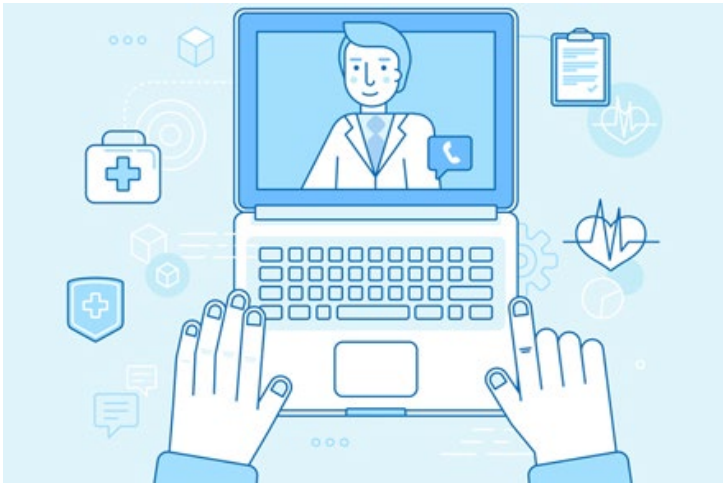
Work from Home

Online Meetings



Many phone calls

Remote Monitoring



Remote Assist –

Bringing Innovation Into Clinical Trials

Regulatory Flexibilities Chart. Overview of regulatory flexibilities across eight health authorities

Country/Health Authority	Enrollment Restart - Submission to HA?*	Temp. Use of Telemedicine - Submission to HA?	Protocol Deviations - Required Actions	Guidance Permits Remote SDR/SDV*	Local Labs - Submission to HA?	Alternative Methods of Consent - Permitted?	Alternative Means of Drug Delivery - Permitted?
Australia	Not Required	Depends on Nature of Deviation or Modification	Notify and/or submit in bulk	Yes	Permitted; Requires notification	Permitted	Permitted; No notification required
Belgium	Notification Only	Depends on Nature of Deviation or Modification	Additional considerations. See comments.	No	Not addressed in guidance	Permitted	Permitted; Additional notification/submission considerations. See comments.
Canada	Notification Only	Not Required	Notification	Not addressed in guidance	Permitted; No notification required	Requires notification and/or approval	Permitted; No notification required
European Union (EMA)*	Notification Only	Not Required	Follow Sponsor's standard procedures	Follows EMA Guidance Under special circumstances	Permitted; Requires notification	Requires notification and/or approval	Permitted; Additional notification/submission considerations. See comments.
Germany	Submission; Approval Required	Depends on Nature of Deviation or Modification	Not addressed in guidance	Under special circumstances	Permitted; Additional notification/submission considerations. See comments.	Permitted	Permitted; Additional notification/submission considerations. See comments.
Japan	Not Required	Not Required	Document	Not addressed in guidance	Permitted; No notification required	Not addressed in guidance	Permitted; No notification required
UK	Not Required	Not Required	Document	Under special circumstances	Permitted; No notification required	Additional considerations	Permitted; No notification required
United States	Not Required	Depends on Nature of Deviation or Modification	Document	Yes	Permitted; Additional notification/submission considerations. See comments.	Permitted	Permitted; Additional notification/submission considerations. See comments.

*HA - Health Authority *EMA - European Medicines Agency *SDR - Source Data Review *SDV - Source Data Verification

Source: Urgent Need for a More Aligned Regulatory Approach for Clinical Trials, DIA Global Forum, 2021

Local Guidance under COVID-19 pandemic

嚴重特殊傳染性肺炎防疫期間藥品臨床試驗執行之建議及原則 released by MOHW
109 年4 月9 日核定
110 年6 月25 日修定

本原則僅於嚴重特殊傳染性肺炎中央流行疫情指揮中心成立期間適用

受試者返診

(一) 提醒各試驗委託者及試驗團隊應以受試者安全及權益為第一優先考量，若無法依原核准之試驗計畫書完成回診、檢驗及評估等項目，試驗委託者應充分考量並評估疫情期間可能帶來之風險與變化，並盡力事先預防及規劃，如受試者決定退出試驗，需尊重受試者意願並記載其退出試驗之原因。
(二) 試驗委託若考量使用替代方式 (如電訪、視訊等方式)執行試驗評估等步驟，請將替代方式變更於試驗計畫書，核准後為之，且應有詳細紀錄以供後續核查。
(三) 若需移轉受試者至另一經核准之試驗機構，程序依該院 IRB 規定為主。若受試者移轉至未核准之試驗機構，除須依該院 IRB 規範外，亦須向本部食品藥物管理署提出新增試驗中心申請，該署將加速審查辦理。試驗機構應留存相關受試者移轉紀錄及核准文件以供後續核查。

Local Guidance under COVID-19 pandemic

試驗藥品之給予

(一) 試驗藥品之給予及運送除須遵循藥事法相關規定外，亦須依循藥品優良臨床試驗作業準則之規範，所有參與試驗執行之人員(包含藥品之調劑及交付)，均應有符合工作資格之教育、訓練及經驗，並經試驗主持人授權臨床試驗相關責任、且應向受試者解釋如何正確使用試驗藥品，因此仍建議由符合前述資格之試驗團隊成員交付試驗藥品予受試者。

(二) 考量疫情期間受試者往返試驗機構之風險及用藥治療需求，可由試驗主持人/協同主持人開立處方箋後，試驗授權藥師依處方箋調劑後交付授權研究護理師運送試驗藥品給予受試者；若為防疫期間緊急狀況下，考量研究護理師之人力及受試者安全，試驗主持人可授權符合藥品優良運銷規範之第三方物流公司，由試驗醫院逕送試驗藥品予受試者。前述事項，應留有授權紀錄。惟皆不適用於在試驗機構施打、服用之試驗藥品。

(三) 試驗藥品給予流程若有變更，應建立SOP，且藥品運送、接收、自受試者處取回餘藥及運送溫度監控等均應有文件紀錄保留，以利日後核查。

嚴重不良事件及試驗偏差之通報

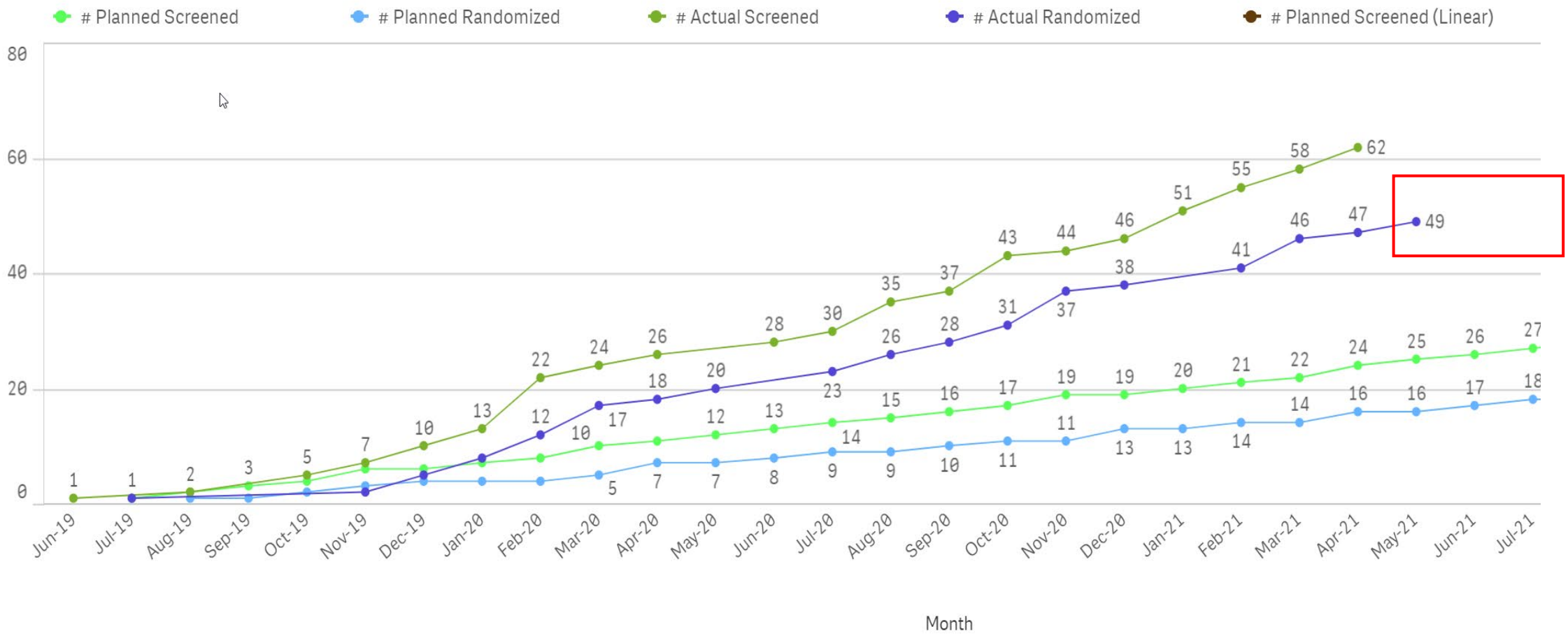
為保障受試者權益及維護試驗品質，建議試驗團隊依試驗計畫書及各機關相關規定進行通報，若因疫情因素或為及時避免受試者遭受傷害所為之偏離或變更，應留有完整相關紀錄供日後核查，並儘快完成通報。

The current practices in APAC countries & other regions (MSD)

- **Taiwan:** No remote access to EMR, live video of medical records are acceptable at some sites; secured emails; certified shared platform sharing (under discussion)
- **Australia** – 50% sites grant remote EMR access based on the CTRA clause. Part of them request guarantee letters complying with site confidentiality policy.
- Korea: No remote access to EMR, live video of the medical records is under discussion
- India – EMR is not available in India. Remote source access has been through webex/certified shared platform sharing of redacted paper source.
- Malaysia – EMRs systems in Malaysia generally do not allow remote access, however, some sites will allow the CRA to take control over webex using the CRAs log in.
- New Zealand - Allows remote EMR access In theory, but they have not had the need
- Singapore/Hong Kong (redacted only) – Not possible to share EMR directly. They would need to print certified copies.
- Thailand – EMR Systems in Thailand generally do not allow remote access. There is only 1 Thailand site allowing CRA to take control via webex. Most are printing off certified copies or sharing paper source and then sharing via Webex.
- **North America** has 95% of sites with remote source data available and 60% of **Canadian** sites (need to sign an additional agreement for remote EMR access for most of sites)
- Latin America: still can go for on-site monitoring under pandemic, but allow remote access to sources when on-site monitoring is not possible (not remote access to EMR due to system issues)
- EU countries: small % of sites are allowing remote access and then only for critical data review in some cases

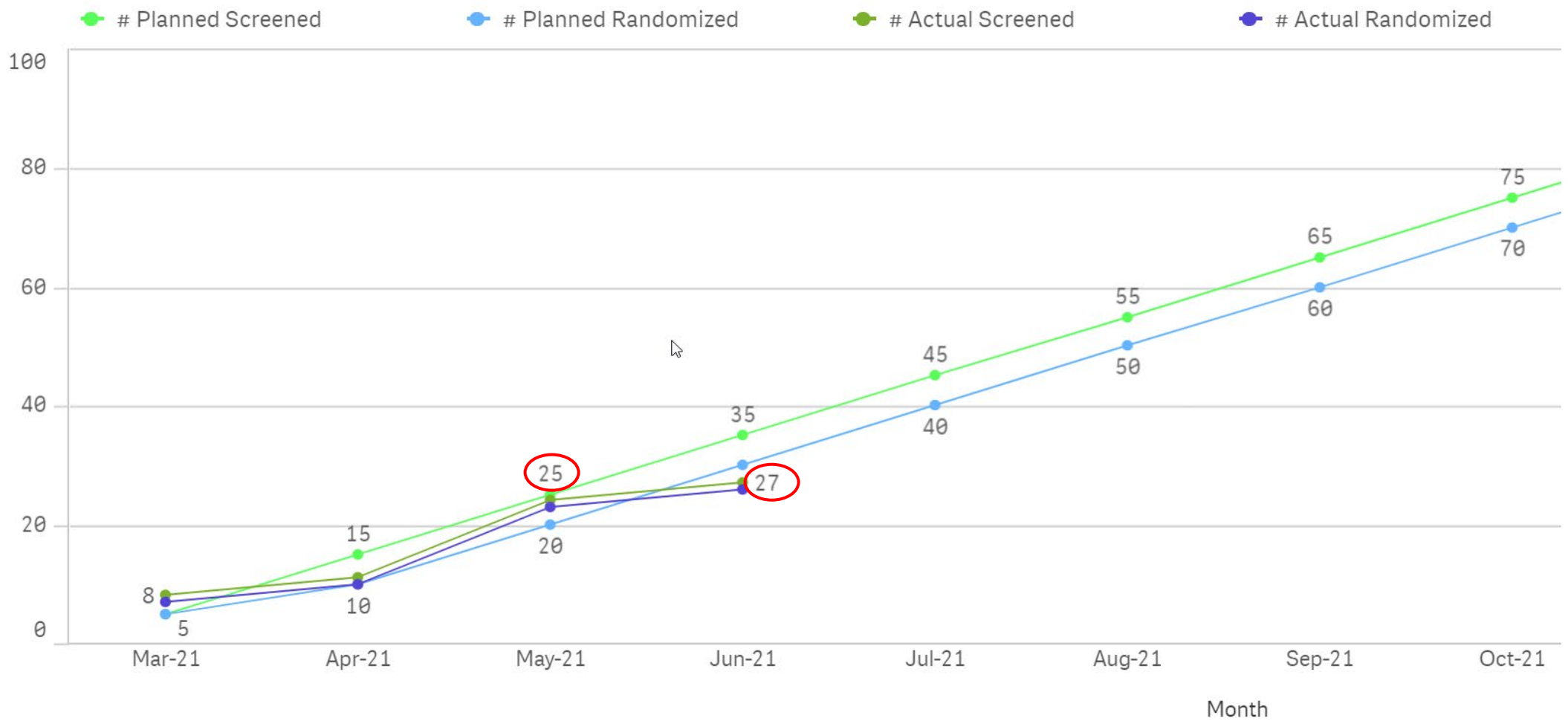
Ongoing phase

Enrolment Progress: Example from one Oncology Study



Ongoing phase

Enrolment Progress: Example of one Vaccine Study



Feasibility Survey

- **Potential Value**

  Remote site validation: e-questionnaire, phone calls, virtual meetings
  - Utilization of virtual Technologies
  - Flexible time and time saving (transportation, WFH)

- **Challenges/Risk**
  - Physical check on facility and equipment (live video tour? Privacy concern: outside business hours)

Site Ready (SR)

- **Potential Value**
  - E-Submission: Accelerate submission process
  - Encourage **remote** trainings, investigator meeting and SIV
  - Regional/ Local Depot: speed up clinical supply importation
- **Challenge/Risk**
  - Paper signature (contract stamping), paper cheques are required at specific sites
  - SR might be delayed if remote site initiation activities are not allowed
  - Site staff availability
  - Effectiveness of remote activities
  - Drug shipment delay (Flight arrangement under COVID-19 impact)
  - Need extra efforts to manage and mitigate logistic issues due to global stock shortage or lengthy shipping time

Ongoing Phase
Study Procedure: Central Lab/Imaging

- Potential Value
  - Certified local lab can be considered
  - Minimize limitation of courier availability & impact from longer turn-around time of lab/imaging reports (if local lab/imaging department can be used)

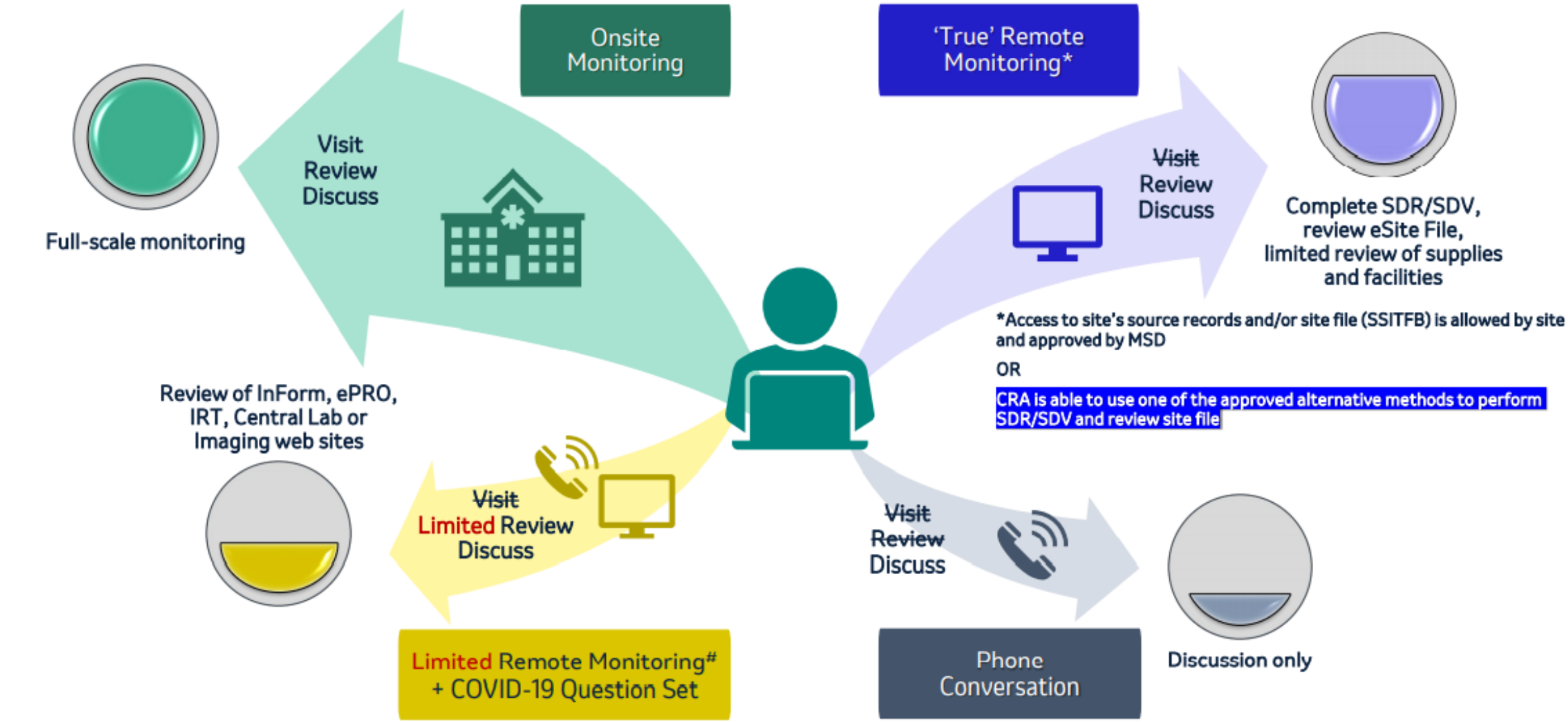
- Challenges/Risk
  - Not all sites capable of implementing this? Is a hybrid model acceptable?
  - How to ensure data that we are collecting is standardized?
  - If patients unable to visit sites, can sampling be done at home and how samples to be shipped to local/central lab? (logistic issue)

Ongoing Phase
Patient Journey: More Home-Centered

- **Potential Value**
  - Patient retention by less travel needs
  - IP shipment without delaying patient treatment – IP **Direct to Patients**
  - Patient pool expansion?

- **Challenges/Risk**
  - Complexity treatment designed study, i.e. oncology
  - Additional study team (physician and nurse) for home visit service, i.e. resource, support by SMO?
  - Expanding study team (more physicians, SCs involved) might increase complexity (Home visits)
  - Allowed per local regulations?

Site Monitoring during COVID-19 Restrictions



#No access to site's source records and/or site file (SSITFB)

Sponsor visit types & Tools

Visit Types	Tools for Remote Completion
PSV	Virtual tours
SIV	Video conferencing
Routine IMV	Electronic source documentation (cloud platforms and EMR); electronic Signature; EDC
Routine audits	Electronic source documentation (cloud platforms and EMR); electronic Signature; EDC

Abbreviations: EDC, electronic data capture; EMR, electronic medical record; IMV, interim monitoring visit; PSV, prestudy site visit; SIV, site initiation visit.

Source: Taking Tele Behind the Scenes: Remote Clinical Trial Monitoring Comes of Age During the COVID-19 Pandemic, ASCO JCO Practice 18Aug2021

Ongoing phase
Monitoring: Remote SDV/SDR

- **Potential Value**
  - Utilization of virtual Technologies
  - Timely communication
  - Less physical visits to site by saving travelling time
  - More Flexibilities for resources location

- **Challenges/Risk**
  - Mix type of source data, i.e. electronic and paper
  - Site-specific privacy requirements
  - Additional burden to site staff to share source documents virtually
  - Long-term applicable?
  - How to ensure data collected is standardized and as accurate as going on-site?

Quality Control
Oversight

- **Potential Value**
  - More Flexibilities for resources location
  - Saving transportation time

- **Challenges/Risk**
  - Some oversight procedures are still required on-site check
  - Lack of F2F interaction, truly reflect the real situation?
  - Communication

Quality Control
Audit/ Inspection

- **Potential Value**
  - Less physical visits to site by saving travelling time
  - More Flexibilities for resources location

- **Challenges/Risk**
  - Additional burden to site staff or monitors to share source documents virtually
  - Pending inspection
  - Lack of F2F interaction, truly reflect the real situation?

eISF

- Site focused, delivering a system that makes managing site documents more efficient. Simply share information with the sponsor. Site has full control of access, no transfer of source documents to Sponsor systems and shared documents can’t be downloaded to Sponsor cloud

Connecting Sites to hundreds of Sponsors & CROs

How other leading Sponsors are working with Florence today

Who provides?

- Sponsors/CROs provide the eISF, but **sites control it and own the data per GCP**

Who pays?

- Ultimately, the Sponsor pays - replacing **document storage and travel line items**

What types of content?

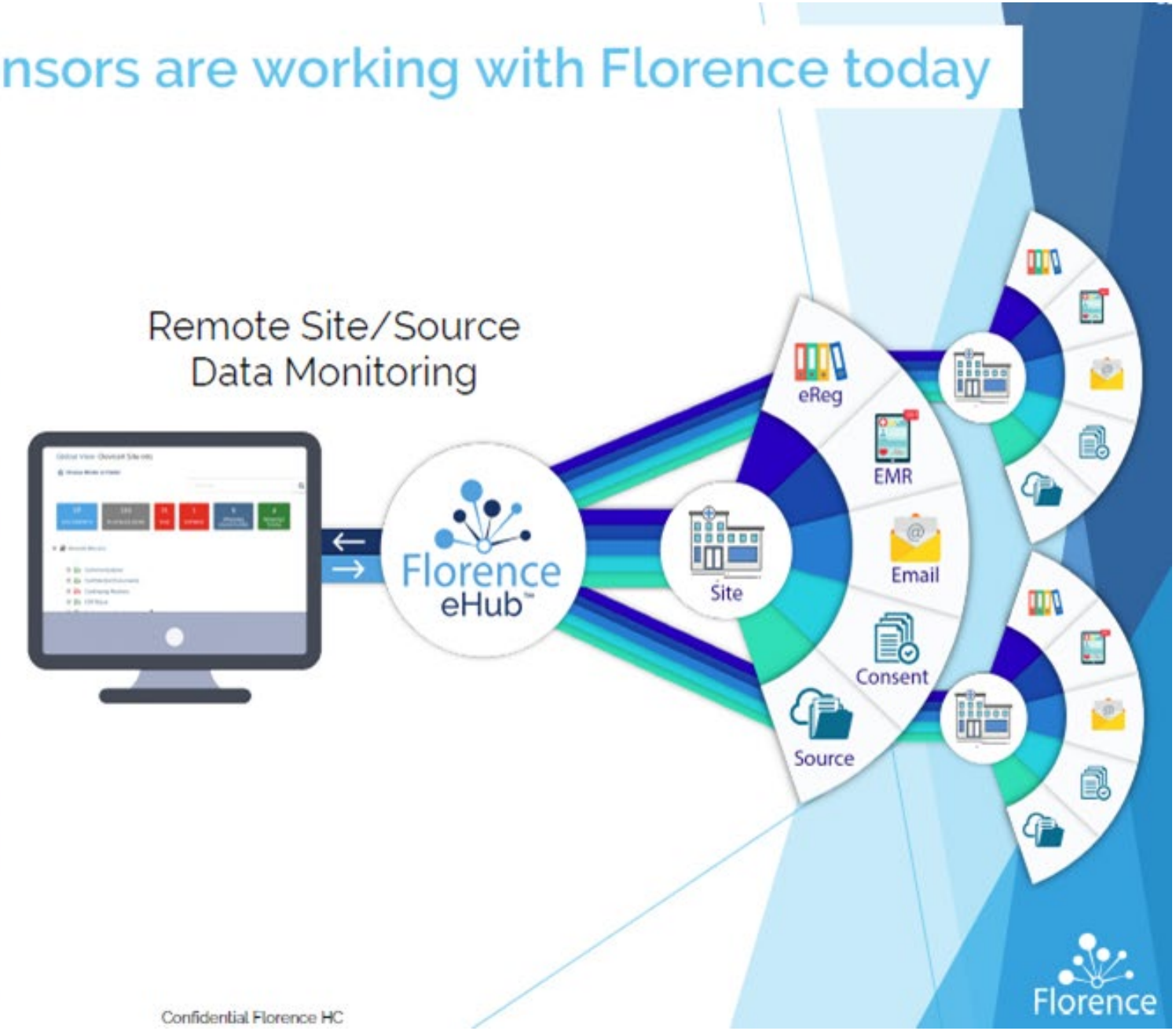
- Scanned, captured and/or created

What about storage?

- Archiving (storage & retrieval) via Amazon Glacier included in eISF fees

What about compliance?

- HIPAA, GCP, US CCPA & GDPR compliant



Recommendations

What can become permanent approaches after COVID?

Recommendation

- **Remote Acess to EMR**

  System opimization, SOPs, Contract/ Agreement, Local regulations
- **Direct to Patient**
- **Telemedicine & Home visits**
- **Digitalization**

  e-signature, e-payment, SIP, eConsent, eLabel, virtual meetings, eISF
- **Standardization across sites?**

Reference: Direct to Patient in Australia (COVID-19)