A Review Of Current Events In The Clinical Research Industry

Embracing Change
Phoenix, Arizona
September 30, 2022
Disclosure

The presenter(s) for today’s session: David Vulcano

☐ I/We have no relevant financial relationship in relation to this educational activity.

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Disclosure

• Presentation is a high level overview. There are lots of additional details, “only ifs” and “except whens”.
• Presentation is a combination of lecture and slides. Neither are intended to be construed as a stand-alone presentation or taken out of context.
• Any opinions put forth in this presentation are not to be construed as the opinions of any particular entity or person (including being the speaker’s own opinions).
Learning Objectives

Upon completion of this presentation, participants should be able to:

• Describe emerging regulatory guidance from FDA and ICH.
• Identify issues and reactions to workforce current challenges and other macroeconomic issues affecting the clinical trials industry.
• Describe the new CMS form required Medicaid coverage of routine care in clinical trials and its complications.
Section 1
New Regulatory Stuff In The Works...
Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (Draft)

- Addresses both hardware and software as Digital Health Technologies (DHT)
- Can be used for Clinical Outcome Assessments (COA/eCOA), For example:
  - Clinician Reported Outcomes (ClinROs/eClinROs)
  - Patient-Reported Outcomes (PROs/ePROs)
  - Observer Reported Outcomes (ObsROs/eObsROs)
  - Performance Outcomes (PerfOs/ePerfOs)
- Sponsor must justify DHT is “fit-for-purpose”
  - Appropriate for the clinical population under study (i.e. education, language, age, physical attributes etc.)
  - Designed for purpose (i.e. size, weight, battery life, alerts such as low battery or data not recorded or transmitted)
  - Advantages and disadvantages of participants supplying their own DHT
    - Sponsor should provide to those who cannot provide their own
  - Evaluation of factors that can affect precision and accuracy
  - Not necessarily meaning FDA Approved/Cleared or even FDA qualified as a “Drug Development Tool (DDT)” or “Medical Device Development Tool (MDDT)
FDA’s DDT and MDDT Qualification Program

• Voluntary program to pre-qualify endpoints
• Provides a regulatory conclusion that the method/material/measurement is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making

• 3 Categories of DDTs/MDDTs
  • Clinical Outcome Assessment
  • Biomarker Test
  • Nonclinical Assessment Model (for MDDTs) / Animal Model (for DDTs)

• Database of “Qualified” (not “Approved” or “Cleared”) DDTs and MDDTs
  • Searchable Database for DDTs: https://fda.force.com/ddt/s/
  • Webpage Link Of Qualified MDDTs: https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt

• FDA has grants available for tool development
DHT Draft Guidance Continued...

- Evaluate Risks For Each DHT
  - Physical, Psychological, Financial, Legal etc. Risks
  - Cost To Subject To Acquire/Use
  - Cybersecurity
  - Vendor Data Use Policies and End-User-License-Agreements Outside of Control of Sponsor (unless modified for the study)

- Sponsor should (among other things)
  - Ensure training of trial participants and trial personnel
  - Develop a plan for technical assistance to trial participants and trial personnel
  - Plan for version control (e.g. patient or personnel updating the software to new version)
  - Safety monitoring plan for abnormal measurements related to patient safety

- Investigators should (among other things)
  - Ensure participants understand what data will be collected and its security and privacy
  - Ensure training of participants on use according to protocol
  - Review data periodically if specified in the protocol
Diversity Plans (Draft)

- Describes content of **Race and Ethnicity Diversity Plan** required by prior guidance
- For INDs, submitted early but no later than End of Phase 2
- For Devices, with IDE application or (for non-IDEs) via special meeting
- Scoped at whole development life-cycle, not just “per-study”
- Encourages use of Real-World-Data and other published literature
Requirements of a Race and Ethnicity Diversity Plan

1. Overview of the disease/condition and its differential characteristics related to race/ethnicity
2. Scope of medical product development program (e.g. differential findings that may be associated with certain racial and ethnic populations)
3. Goals for enrollment of underrepresented racial and ethnic population
4. Specific plan of action to enroll and retain diverse participants...including but not limited to:
   • site location and access (e.g., language assistance for persons with limited English proficiency, reasonable modifications for persons with disabilities, and other issues such as transportation);
   • sustained community engagement (e.g., community advisory boards and navigators, community health workers, patient advocacy groups, local healthcare providers, etc.);
   • reducing burdens due to trial/study design/conduct (e.g., number/frequency of study-related procedures, use of local laboratory/imaging, telehealth);

   Describe metrics to ensure that diverse participant enrollment goals are achieved and specify actions to be implemented during the conduct of the trial(s) or studies if planned enrollment goals are not met.

5. Status of meeting enrollment goals (as applicable)
   • As the diversity plan is updated (when applicable), discuss the status of meeting enrollment goals.
   • If the sponsor is not able to achieve enrollment goals despite best efforts, discuss a plan and justification for collecting data in the post-marketing setting.
Some Practices Identified By FDA and Industry

• Site Knows Demographics Of Local Community And Database Metrics
• Site And/Or Sponsor Has Outreach Program In Specific Communities
• Site Staff Is Culturally Representative
  • Race/Ethnicity
  • Trained In Proper Language/Pronunciations If Not Fluent In Subject Language
• Sponsor/CRO Provides Pre-Made Or “Just-In-Time” Translated Documents
  • Informed Consent, Recruitment Documents, Protocol Instructions, E-diaries etc.
  • All Pre-approved By IRB.
• Advertisement Efforts Use Appropriate Media Outlets
• Vendors Of Subject-Facing Technology Have Multilingual Helpdesk
• Protocol is “Location Agnostic” Infrastructure Exists To Support It (e.g. Mobile Health Professionals, Patient Monitoring Technology, Mobile Radiology Units etc.)
• Sponsor/CRO Offers More Robust Transportation Assistance, Financial Support
• Stipends Are Adequate, Paid Timely And In A Manner Acceptable To The Population (e.g. Unbanked Population Have Difficulty Cashing Checks)
Remote FDA Regulatory Assessments (Draft)

• “Assessments” are not “Inspections”
  • No Form 482 or Form 483 which are for inspections only
• Mandatory for some (manufacturers, compounding) but voluntary for others (clinical investigators, IRBs)
• Responses to FDA requests electronically via their portal or via mail if paper copy is only option
• FDA will send notifications of findings (but no Form 483) and will accept responses to those findings for up to 15 business days.
• Refusing a voluntary RRA “will not result in an enforcement action” … but FDA “may consider other actions to [get information] such as inspection.”
Temporary Allowances Still in Effect Until Emergency Is Declared Over BY Federal Government

Key Issues

- Remote consent and signature alternatives
- Remote patient monitoring/visits
- Remote study monitoring


ICH-E6(R3): The Next Generation of GCPs

• Still a Work-In-Progress (Workproducts Delayed Due To COVID)
• A “full rewrite and reorganization of the ICH E6(R2) Guideline” with 3 sections
  1. Overarching Principles and Objectives Document
  2. Annex 1: Interventional Clinical Trials
     • For “Use of unapproved or approved drugs in a controlled setting with prospective allocation of treatment to participants”
     • Essentially, with Section 1, the full replacement of ICH E6(R2)
  3. Annex 2: Additional Considerations For Non-Traditional Interventional Clinical Trials
     • For designs such as pragmatic and/or decentralized as well as trials that incorporate real-world data sources etc.
     • Completely new section
Demands From The Field of The ICH Working Group For R3

• Remote Informed Consent And Accompanying Technology
• Non-Traditional Trial Design, Data Sources (e.g. RWD, Wearables) And Decision Support (e.g. Predictive Algorithms And Artificial Intelligence).
• Remote Source Document Verification
• Patient Engagement From Study Design To Conduct
• PI Oversight In Decentralized Trials / Definition Of Sites
• More Elaborations On Risk-based And Centralized Monitoring
• Remote Inspections
• Conceptually Change “Essential Documents” To “Essential Information”
Section 2
Workforce Challenges

WHEN THE RECEPTIONIST SHOWS UP TO WORK TO FIND OUT THAT THEY ARE NOW A CRC
Study Cash Flow: Site’s Cost Are Rapidly Increasing At High Rates

- Current pressures leading to people exiting the workforce

- Affects Current Studies
  - Site Difficulty In Getting Sponsors/CROs To Adjust Budgets
  - Affects Negotiating New Studies
  - "Fair Market Value" ranges set at pre-problem numbers

- Affects Future Costs (supplies, overhead etc)
- Affects Future Value Of Money (i.e. multi-year studies)
- E.g. A $100 Line-Item Budget Item In Year 3 Is Worth The Following In Today’s Dollars
  - ~$95 Under 1.7% inflation (the average inflation the past decade)
  - ~$80 Under 7.9% inflation (current U.S.BLS number as of March 2022).

- CROs and Health Providers Recruiting CRCs Away (Due To Their Resigning Employees)
  - Offering larger salaries, sign-on bonuses, referral bonuses, benefits etc.

- "The Great Resignation"
- Staff Migration
- Failure To Adjust
- Inflation @ 40 Year Highs

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What job function do you see the largest reduction and hiring challenge?

94%

Site Coordinators

What is the main cause of this workforce challenge?

- Not enough trained or experienced individuals in the job pool
- Financial ability to compensate employees
- Employees leaving for better opportunities (e.g. CRO, health system)

Source: SCRS 2021 Site Landscape Survey
Difficult Choices Due To Loss of A CRC

• Withdraw Of Existing Subjects (i.e. Cannot Do Safety Visits)
• Subjects Withdrawing On Their Own (i.e. Losing Personal Connection to CRC)
• Halting New Enrollment
• Reallocation of Quality Resources
  • Supervise/Train New & Lesser Experienced Staff
  • Less Resources To Provide Same Level of QA/QI
• Closing Challenging and/or Under-Budgeted Studies
What can Sponsors and CROs do to help alleviate this challenge? Select all that apply.

**Most Selected Request (47%)**
- Provide adequate trial budgets to support hiring/retaining of staff

**3-way Tie (~18%) For Second Most Selected Request**
- Keep trial opportunities active and flowing
- Provide support to train and raise new research personnel
- Provide resources and support for job searching or applicant marketing

Source: SCRS 2021 Site Landscape Survey
Non-Salary Related Best Practices Shared

• Hold “Stay Interviews”, Not Just Performance Reviews
• Add Customized/Non-Traditional Benefits
• Workforce Recognition Software
• Work-Life Fluidity Options (Not Work-Life Balance but Fluidity)
  • Non-Traditional Hours
  • Shift Of Locations
• Moving Past “2 Years Experience Required”
  • Look For Skills, Not Experience
  • More In-House Training
• Caution For Increased Resume/Interview Fraud
Site’s Ask of Sponsors/CROs

• Have Open Dialogue With Sites On This Issue
  • Understand Site Staff Turnover, Regardless Of Reason, Impact On Studies
  • Understand CRA/Monitor/Project Manager Turnover’s Impact On Sites

• Help With Solutions
  • e.g. Sponsor Can Require “Study Continuity Plan” if CRO/Sponsor Hires Away Site CRCs
  • Provide Site Additional Resources As Appropriate

• Encourage Sponsors/CROs to Share Successes in Alternatives To The “2 Years Experience”
  • Opens Up Applicant Pool Instead Of Targeting CRCs
  • E.g. In-House Training, Academic Degrees, Similar Skillsets From Non Life-Science Areas
Other Macroeconomic Headwinds

• Supply Chain Issues
• New Environmental/Social/Governance (ESG) Demands On Businesses
• Geopolitical Tensions
• Inflation Outpacing Fair Market Value Databases
## Line Item Annual Cost Of Living Adjustment Calculations (Simplified Estimate)

### Input Your Variables Here...

- **Line Item Amount**: $1,000.00
- **Projected Annual Inflation Rate**: 8.60%
- **Number of Years In Future (Up to 20)**: 5

### ...And Your Options Are Here.

#### Option 1: Annually Adjusted Amount

<table>
<thead>
<tr>
<th>Year</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1,000.00</td>
</tr>
<tr>
<td>2</td>
<td>$1,086.00</td>
</tr>
<tr>
<td>3</td>
<td>$1,179.40</td>
</tr>
<tr>
<td>4</td>
<td>$1,280.82</td>
</tr>
<tr>
<td>5</td>
<td>$1,390.97</td>
</tr>
</tbody>
</table>

#### Option 2: Stable Amount Averaged Out To Accommodate Adjustments

- A payment of $1,000.00 for a line item...
- ...over the projected number of 5 years...
- ...averages out at $1,187.44 per payment.
Input Payment Variables Here...

- Line Item Amount: $1,000.00
- Projected Annual Inflation Rate: 8.60%
- Number of Years Until Holdback Paid: 5.0
- Holdback Percent: 10%

...And The Impact Is Indicated Below.

**COLA Estimates If Payments Are Made Quarterly Instead Of Monthly**

- Instead of contracting for $1,000.00...
- the Site is essentially only contracting for $985.82...
- so to be made whole from this demand the Site needs at least $1,014.38

**COLA Estimates If There Are Holdbacks**

- The holdback from $1,000.00...
- is $100.00...
- which at the approximate end of the study is only worth about $66.20...
- thus the Site is essentially only contracting for $966.20...
- so to be made whole from this demand the Site needs at least $1,051.06

**COLA Estimates for Both Quarterly Payments And Holdbacks**

- The holdback from $1,000.00...
- is $100.00...
- so the Site would be first paid $900.00...
- but adding 2 months lag to that payment makes that actually worth $887.24...
- and, when actually paid, the amount held back is actually worth $66.20...
- thus the Site is essentially only contracting for $953.44...
- so because today's value of the delayed payment is $912.95...
- and today's value of the holdback is $151.06...
- to be made whole from this demand the Site needs at least $1,064.01
Section 3
Decentralization Of Trials

Tell me the truth. I'm... I'm ready to hear it.

Decentralized trials can be a viable option for patients AND sites.
Infrastructure Allows For Flexibility
i.e. Build The “Site” Around The Subject (As Appropriate)

Subject #1 works next door to clinic and can take time off.

Subject #2 lives 120 miles away and cannot come to the clinic for most visits, if any.

Subject #3 travels for work which conflicts with several visits.

Subject #2
Clinic
Mobile Health
Tele-med

eConsent
IP Home Delivery

Subject #3
Clinic
Local Health Provider
Tele-med

e.g., EKG, labs, weight as they are not bringing their study supplied Bluetooth scale on the trip for daily weight
In 2020-2021, were you approached by a sponsor or a CRO to conduct a decentralized-type trial?

- Yes, 66%
- No, 33%

Did you Participate?

- Yes, 80%
- No, 20%

Source: SCRS 2021 Site Landscape Survey
Why did you participate?

TOP ANSWERS
• Desire to bring my site into the future
• Would be beneficial to the patient population

LEAST PICKED ANSWERS
• Financially Beneficial
• Technology used was simple and easy for our site to utilize

Why Didn’t you Participate

TOP ANSWERS
• Didn’t have the patient population
• Patient safety concerns

LEAST PICKED ANSWERS
• Not comfortable with this type of trial
• Legal or insurance issues

Source: SCRS 2021 Site Landscape Survey
What are you doing now, or planning to do, to prepare for decentralized trials? Select all that apply

Source: SCRS 2021 Site Landscape Survey
What **would you expect** to be the **biggest** challenges if you would participate?

1. Financial Compensation
2. Legal or Insurance Issues
3. No Challenges Expected
4. All Other Responses

What **have you experienced** to be the **biggest** challenge?

1. Financial Compensation
2. Having the Capital To Invest In Own Tech
3. Having the Necessary Staff To Implement
4. All Other Responses

Source: SCRS 2021 Site Landscape Survey
Do you feel that training for trials with decentralized elements take more time than those without decentralized elements?

- Yes, 62%
- No, 18%
- Unsure, 21%

How much estimated time in number of hours does your site spend, per month per trial on average, on training for trials with decentralized elements as compared to a trial without decentralized elements?

Average – 17.5 hours per month, per trial

Source: SCRS 2021 Site Landscape Survey
When it comes to technology use preferences in 100% decentralized and hybrid decentralized trials, which of the following applies most directly to your site?

- 54.67%: We prefer to use all of our own technology
- 13.33%: We prefer to use a mix of our technology and technology made available by the sponsor/CRO
- 32.00%: We prefer to use technology made available by the sponsor/CRO

Source: SCRS 2021 Site Landscape Survey
What does your site want or need in the form of support from Sponsors and CROs in regards to participation in decentralized or hybrid decentralized trials? Select all that apply (Top 3)

- Stronger and more robust budgets: 66.67% Most Important, 17.54% 2nd Most Important, 15.79% 3rd Most Important
- Technology implementation guidance: 45.16% Most Important, 32.26% 2nd Most Important, 22.58% 3rd Most Important
- More effective patient technical support: 42.86% Most Important, 22.86% 2nd Most Important, 34.29% 3rd Most Important
- Robust and thorough patient training materials and resources: 41.36% Most Important, 34.48% 2nd Most Important, 24.14% 3rd Most Important
- Integrated and consistent technology: 38.00% Most Important, 36.00% 2nd Most Important, 26.00% 3rd Most Important
- Assistance understanding regulatory requirements: 34.29% Most Important, 42.86% 2nd Most Important, 22.86% 3rd Most Important
- Robust and thorough site personnel training: 31.25% Most Important, 34.38% 2nd Most Important, 34.38% 3rd Most Important
- More effective site technical support: 28.57% Most Important, 34.29% 2nd Most Important, 37.14% 3rd Most Important
- Other: 25.00% Most Important, 62.50% 2nd Most Important, 12.50% 3rd Most Important

Source: SCRS 2021 Site Landscape Survey
The site PI is not really in charge of the study anymore

CHANGE MY MIND
Today’s “Site PI”…
• ...Is Now A Sub-I
• Is Responsible Only For Compliance/Quality/Data Generated From Their Location

Sponsor/CRO Is Now Regulatory Responsible For...
• Remote Patient Monitoring Implementation & Tech Support
• Mobile Health Professionals’/Services’ Compliance & Quality
Section 4
New Medicaid Requirements
210(a)(3)(c) of the Consolidated Appropriations Act of 2021

• Desired to clarify that Medicaid must cover the *routine care* costs in *qualifying clinical trials*
  • Must Also Cover “Out Of State” and “Out Of Network” Routine Care In Clinical Trials
  • State cannot require submission of the protocols or other proprietary information of the qualifying clinical trial

• Added a requirement for a form for each patient signed by both PI and a healthcare provider to be able to bill Medicaid
  • Compliance date for the form was Jan 1, 2022
  • Form not published by CMS until July 1, 2022
  • Up To States To Implement In Their Own Way
“Routine Care” Defined

• “i) any item or service provided to prevent, diagnose, monitor, or treat complications resulting from such participation, to the extent that the provision of such an item or service to the individual outside the course of such participation would otherwise be covered under the State plan or waiver; and (ii) any item or service required solely for the provision of the investigational item or service that is the subject of such trial, including the administration of such investigational item or service;”

• Does not include
  • (i) an item or service that is the investigational item or service that is— ‘
    • (I) the subject of the qualifying clinical trial; and (II) not otherwise covered outside of the clinical trial under the State plan or waiver; or ‘
  • (ii) an item or service that is—
    • (I) provided to the individual solely to satisfy data collection and analysis needs for the qualifying clinical trial and is not used in the direct clinical management of the individual; and
    • (II) not otherwise covered under the State plan or waiver.”
“Qualifying Clinical Trial” Defined

• “(i) The study or investigation is approved, conducted, or supported (which may include funding through in-kind contributions) by one or more of the following: ‘
  • The National Institutes of Health
  • The Centers for Disease Control and Prevention
  • The Agency for Healthcare Research and Quality
  • The Centers for Medicare & Medicaid Services
  • A few other federal entities
  • A cooperative group or center of any of the entities described in subclauses (I) through (IV) or the Department of Defense or the Department of Veterans Affairs.
  • A qualified non-governmental research entity identified in the guidelines issued by the National Institutes of Health for center support grants.

• “(ii) The clinical trial is conducted pursuant to an investigational new drug exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act or an exemption for a biological product undergoing investigation under section 351(a)(3) of the Public Health Service Act. (iii) The clinical trial is a drug trial that is exempt from being required to have an exemption described in clause (ii).”
Final Version Of Form

• Much more user friendly than the original draft.
• Allows for PI to also sign as HCP
• 56 hours to complete???
Key Questions Left To The States…

• Can a form be signed in counterparts (i.e. one signature signed locally and another supplied by fax or email scan which collectively is two signatures)?

• Must the form be signed PRIOR to enrollment in the trial and obtaining routine care services or can it be signed after services are rendered?

• Must the Healthcare Provider be a physician or can other disciplines (i.e. Nurse Practitioner) sign in that capacity?

• What are we supposed to do with the form? Is it to only be housed in the patient’s record or is it to be submitted with the bill?

• The law requires the form effective January 1, 2022 however the form was not published until July 1. Are sites/providers required to obtain a form to attest for services provided January 1, 2022 through June 30, 2022? Or is this only effective July 1 or another date?

• Can you confirm that this form is required for items and services billed on or after July 1, regardless of when the patient was enrolled? For example if a beneficiary was enrolled in a qualifying clinical trial in 2020 and will receive routine care services in August of 2022, will a form be required?
Don’t Like This New Requirement?

• To eliminate the form requires, *literally*, an act of congress.
  • New legislation or tack on to existing bill
• Write to your representative(s) if you think the form needs to go away
  • [https://www.congress.gov/members/find-your-member](https://www.congress.gov/members/find-your-member)
…Thank you!

Questions?
Comments?
Other Issues?