Developing and planning multi-center clinical trials

CTSI Research Career Development Seminar
Multisite Trial Development and Implementation Miniseries

Hosted by the Clinical Research Support Center (CRSC) and
CTSI's Research Education, Training, and Career Development core (CTSI-Ed)

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Driven to Discover℠

Developing and planning multi-center clinical trials

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Objectives

- Learn about establishing and maintaining study teams

- Standardization of procedures across sites, with a focus on safety and efficacy endpoints

Study teams

- There are multiple groups of individuals typically involved with the conduct of multi-site trials, some established just for the trial, others likely existing prior to initiation of the trial:
  1. Protocol team
  2. Safety and regulatory team
  3. Clinical monitoring team
  4. Data management team
  5. Laboratory team
  6. Data and safety monitoring board
  7. Site investigators
  - Not comprehensive: depends on the study

Protocol team

- Central to any trial is the establishment of a **protocol team**
  - This is a group of scientists responsible for making decisions regarding major features of the study design
  - The goal of the group is to develop a protocol document via consensus building
  - This entails determination of major issues: e.g., type of intervention, randomization, controls, endpoints, assessments, sample size
- Usually includes clinicians, statisticians, and laboratory scientists
- Typically have meetings at least once a week while protocol is being developed and periodically once study underway
- This team is usually specific to a study

Pre-existing teams

- One should try to use pre-existing teams for many of the trial functions to take advantage of systems already in place

- For example, there are organizations that support clinical coordinating activities and/or data coordinating activities

  - These organizations would already have systems in place for many of the required collaborating groups of individuals

  - Contract research organizations are businesses that provide this type of support

  - There are academic groups that also provide this support-in this case, expect to include individuals from these groups on the protocol team

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Operations team

- A common distinction is between the protocol team and the operations team

- The operations team picks up where the protocol team leaves off-how to implement the protocol

- Typically this team also meets once a week once the protocol is drafted
  - These are usually large meetings with the protocol chair, safety monitors, pharmacists, data management staff, regulatory personnel, study coordinators, statisticians, laboratory personnel, …

- The distinction between operations and science is not always clean-cut

Site investigators

- Site investigator meetings are useful for studies with more than a small number of sites
- These meetings focus on issues common to all sites without too much detail on issues best handled on a site-by-site basis
  - Current enrollment, highlighting sites doing very well
  - Changes to the protocol (new or proposed)
  - Review new science relevant for the protocol
  - Current state of forms collection across all sites with a focus on completeness
  - Review outstanding queries across all sites

Standardization of procedures across sites

- There are several opportunities to standardize procedures across sites:
  1. Write a protocol that is amenable to standardization across sites
  2. Design straightforward data collection procedures
  3. Develop a high-quality manual of procedures (MOP) with a high level of detail
  4. Provide centralized training, or train the trainer type training for material described in the MOP
  5. Provide continual access to the MOP and training materials
  6. Clinical site monitoring

Standardization of endpoints across sites

- Many safety and efficacy endpoints are event driven, hence careful definition of events is essential for the scientific integrity of the trial

- Some of the difficulties here can be avoided at the protocol development stage, e.g., cause of death is frequently problematic, but all cause mortality is not

- An **Endpoint Review Committee** can be useful when definition of endpoints can be subjective (e.g., the occurrence of an AIDS defining event)

Endpoint review committee

- Components of a well-designed endpoint review committee
  - Independent, experienced clinicians
  - Clearly defined diagnostic criteria for various outcomes
  - Good documentation of clinical circumstances around the event
  - Blinding of treatment group data
  - Decision made by vote of committee members

Thank you

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Multisite seminar series

Objectives:

- Secure data collection, transfer and storage
- Importance of data management plan

by Amutha Muthusamy, M.Sc, CRTI Process Manager, Data Solutions Group, Masonic Cancer Center

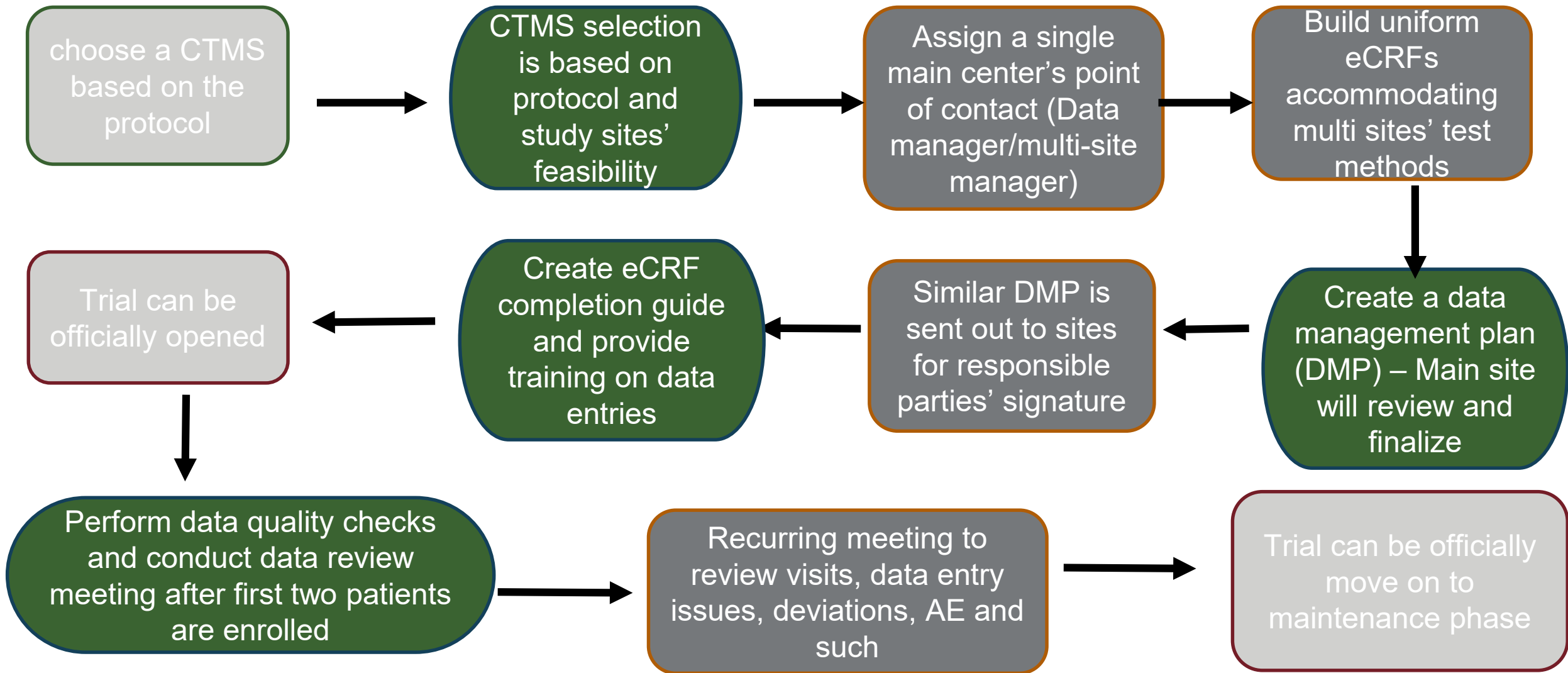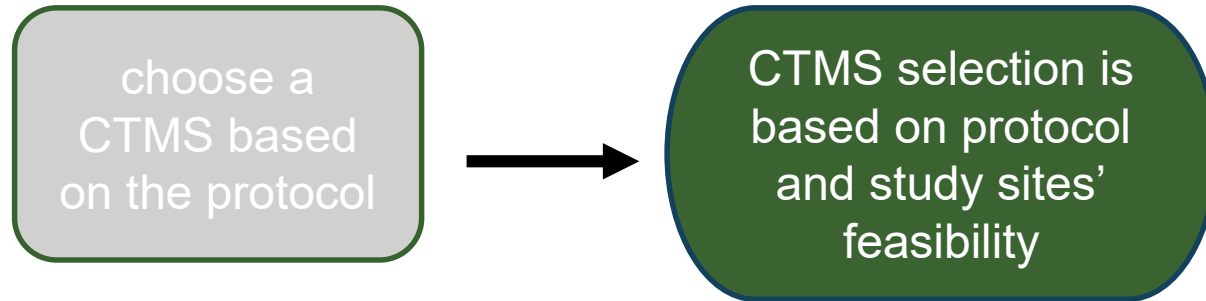*"Data that is loved tends to survive." – Kurt Bollacker*

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Multisite data management workflow

choose a CTMS based on the protocol → CTMS selection is based on protocol and study sites' feasibility → Assign a single main center's point of contact (Data manager/multi-site manager) → Build uniform eCRFs accommodating multi sites' test methods

Create a data management plan (DMP) – Main site will review and finalize ← Similar DMP is sent out to sites for responsible parties' signature ← Create eCRF completion guide and provide training on data entries → Trial can be officially opened

Trial can be officially opened → Perform data quality checks and conduct data review meeting after first two patients are enrolled → Recurring meeting to review visits, data entry issues, deviations, AE and such → Trial can be officially move on to maintenance phase

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Choosing a clinical trial management system

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┌─────────────────┐         ╭─────────────────╮
│                 │         │                 │
│   choose a      │         │ CTMS selection  │
│   CTMS based    │ ──────▶ │ is based on     │
│  on the protocol│         │ protocol and    │
│                 │         │ study sites'    │
│                 │         │   feasibility   │
└─────────────────┘         ╰─────────────────╯
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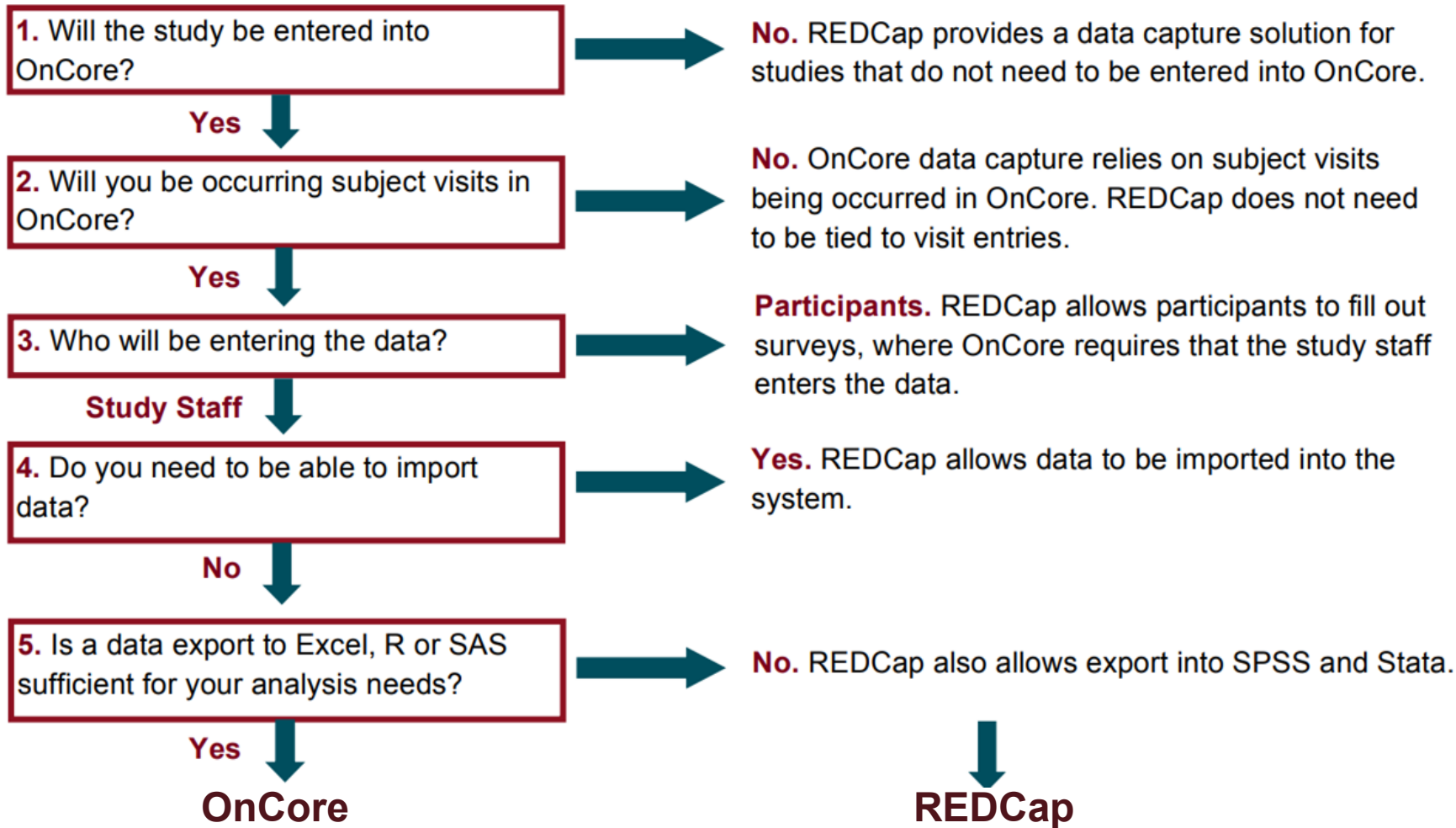
- Identify the data collection and management system
- Check with multi sites feasibility on the chosen system
- Training can be offered to use a uniform data management system
- Consider HIPAA complaint systems for secure data collection, transfer and storage

Clinical trial management systems to consider

- REDCap and OnCore are two such CTMS and both are HIPAA compliant
- They enable secure networks
- Data entered in here are encrypted, tracked and audited
- They allow access to multiple coordinators at different sites
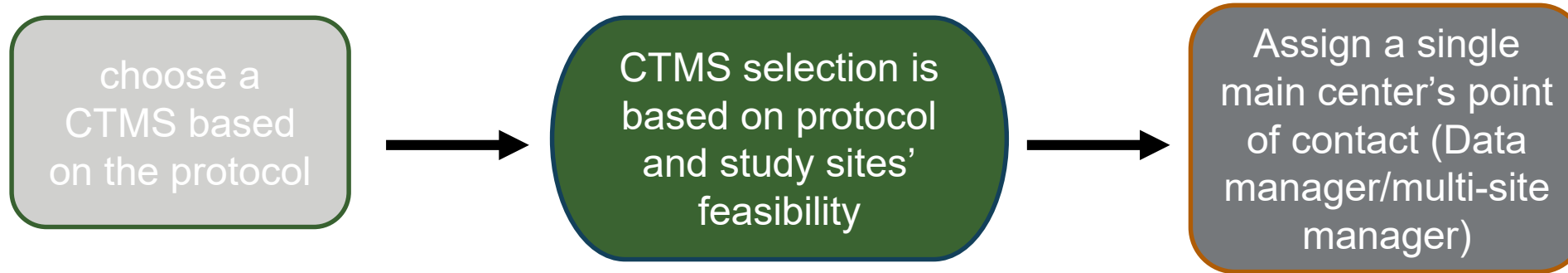- The access rights can be restricted to authorized persons only
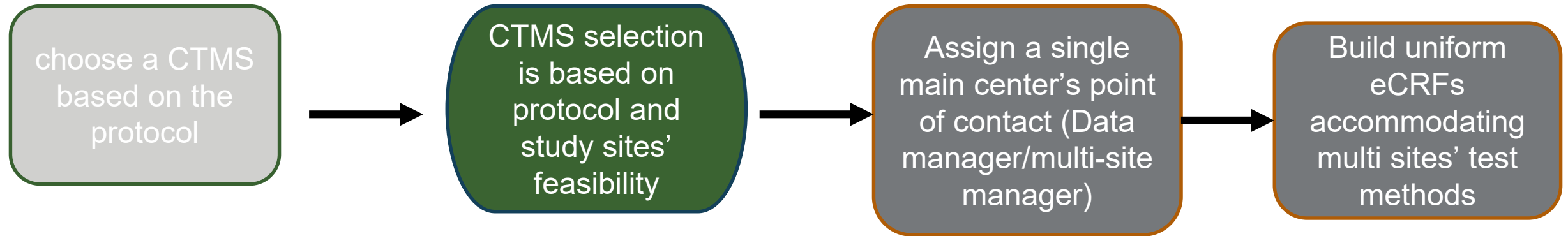
Choosing the right data management system

1. Will the study be entered into OnCore?	**No.** REDCap provides a data capture solution for studies that do not need to be entered into OnCore.
↓ **Yes**	
2. Will you be occurring subject visits in OnCore?	**No.** OnCore data capture relies on subject visits being occurred in OnCore. REDCap does not need to be tied to visit entries.
↓ **Yes**	
3. Who will be entering the data?	**Participants.** REDCap allows participants to fill out surveys, where OnCore requires that the study staff enters the data.
↓ **Study Staff**	
4. Do you need to be able to import data?	**Yes.** REDCap allows data to be imported into the system.
↓ **No**	
5. Is a data export to Excel, R or SAS sufficient for your analysis needs?	**No.** REDCap also allows export into SPSS and Stata.
↓ **Yes**	↓
OnCore	**REDCap**

https://ctsi.umn.edu/sites/ctsi.umn.edu/files/2021-03/oncore-vs-redcap.pdf

Dedicated study staff

choose a CTMS based on the protocol	→	CTMS selection is based on protocol and study sites' feasibility	→	Assign a single main center's point of contact (Data manager/multi-site manager)

- Consider assigning a dedicated resource, data manager/multi site manager from the main site

- Having a dedicated point of contact will be helpful to ensure uniform data capturing methods are followed

- The point person can also help with frequently asked questions on data entries and can help with protocol / data collection clarifications

- Can maintain a delegation log for multi sites separately to keep track of all the responsible parties from the participation sites

Considerations during the eCRF design

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│ choose a CTMS  │      │ CTMS selection │      │ Assign a single│      │ Build uniform  │
│ based on the   │ ───▶ │ is based on    │ ───▶ │ main center's  │ ───▶ │ eCRFs          │
│ protocol       │      │ protocol and   │      │ point of       │      │ accommodating  │
│                │      │ study sites'   │      │ contact (Data  │      │ multi sites'   │
│                │      │ feasibility    │      │ manager/multi- │      │ test methods   │
│                │      │                │      │ site manager)  │      │                │
└────────────────┘      └────────────────┘      └────────────────┘      └────────────────┘
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"*Without a systematic way to start and keep data clean, bad data will happen.*" — *Donato Diorio*

- If we have a tool let's use it to the fullest
- consider using design experts
- spend time to look at the data elements closely
- Consider adding validations such as paying attention to number/text fields, options, calculated fields, validations to restrict data entry errors, add data quality rules and measures to the design

Examples of validations

Complete Blood Count (CBC)

CBC	Result
WBC (10th to the 9th/L)	0
	Validation Error: The value is lower than the normal range. Please review and confirm

Examples of validations

3. Disease Progression?

◉ Yes

○ No

○ Unknown

4. If Disease Progression, list date of progression

Validation Error: The answer is selected as 'YES' to disease progression. So, please enter the date here. Donot leave it blank

Considerations during the eCRF design - contd.,

- Discuss with sites on the test, test methods, units and make sure
  to give additional room in the eCRFs to add additional comments

- The consistency and standardization of eCRF designs are important to collect clear and relevant information.

Data management plan

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┌──────────────┐      ┌──────────────┐      ┌──────────────┐      ┌──────────────┐      ┌──────────────┐
│ choose a     │      │ CTMS selection│     │ Assign a single│    │ Build uniform │     │ Create a data │
│ CTMS based   │ ───▶ │ is based on   │ ───▶│ main center's  │───▶│ eCRFs          │───▶ │ management     │
│ on the       │      │ protocol and  │     │ point of       │    │ accommodating │     │ plan (DMP)    │
│ protocol     │      │ study sites'  │     │ contact (Data  │    │ multi sites'   │     │               │
│              │      │ feasibility   │     │ manager/multi- │    │ test methods   │     │               │
│              │      │               │     │ site manager)  │    │                │     │               │
└──────────────┘      └──────────────┘      └──────────────┘      └──────────────┘      └──────────────┘
```

- After eCRFs creations main site PI and statistician and other responsible parties can sign off on the design with a data management plan
- Data management plan should include

    - protocol details

    - protocol endpoints

    - statistical analysis plan

    - DLT/SR reporting method

    - list of case report forms

    - list to detail case report forms based on visits

    - sample collection details

    - timeline of case report forms completion

The participating site will be given a similar DMP with participating PI, coordinators sign off fields

eCRF completion guide and training

Create a data management plan (DMP) → Similar DMP is sent out to sites for responsible parties' signature → Create eCRF completion guide and provide training on data entries
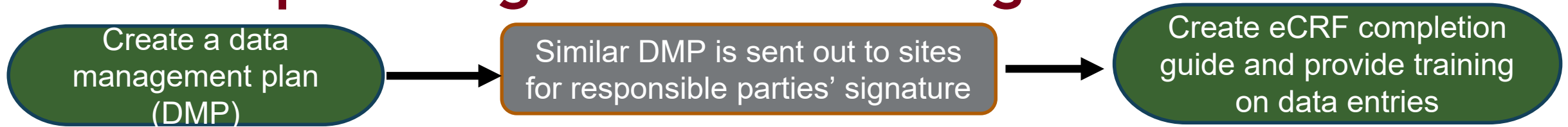
- Main site needs to provide an eCRF completion guide to give clear instructions on how to complete eCRFs, best practices, and a separate section on frequently asked questions.

- Having a documented codebook, data dictionary, eCRF completion guides are important ways to ensure data collection is consistent and uniform across sites. The participating sites need to be trained on how to complete the eCRFs, occurring visits, procedures

- Documenting the standardized subject identifiers / Subject ID assignment (uniform ID assignment) is necessary
- The training involves showing the participating coordinators the main site's best practices on data entries.

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Data review meetings and recurring meetings

Trial open to accrual → data review meetings → Recurring meetings

- After two patient's data entries are made, the lead site can arrange for a meeting to review the data entry methods for accuracy, consistency, and completeness is a good idea

- Before this meeting a data quality check and a QC report can be generated to go over all of the eCRF completion guidelines and to address issues with data entries if any

- A periodic standing meeting with participating sites is also advisable to review enrolled subject counts, visits, pending form completions and address s enrollment.

Trial can be officially move on to maintenance phase

Contact details

Data Solutions Group, Cancer Research Translational Initiative, Masonic Cancer Center
CRTI director: Deepa Kolaseri

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dsg1@umn.edu

Website: https://z.umn.edu/CRTI-DSG

Partners:

https://cancer.umn.edu/researchers/resources/clinical-trials-office

https://ctsi.umn.edu/services/data-informatics/biomedical-informatics-and-data-access

https://cancer.umn.edu/translational-therapy-shared-resource

Useful resources

- https://ctsi.umn.edu/services

- https://ctsi.umn.edu/tools/oncore-ctms/about-oncore

- https://ctsi.umn.edu/tools/redcap

Biospecimen support

Provides high-quality, centralized biospecimen research support while ensuring patient care and confidentiality.

Budgets and finances

Support from financial professionals who can negotiate, analyze, recommend, and regularly review the financial components of a clinical trial.

Community-engaged research

Support for conducting community-engaged research, including expert consultations and assistance finding research partners in the community or at the University.

Data and informatics

Direct access to clinical data from the electronic health records of more than 2 million patients and support from data analysts in extracting and managing that data.

Multi-site study support

Assistance conducting multi-site clinical trials; multiple resources are available, including the Trial Innovation Network (TIN), Midwest Area Research Consortium for Health (MARCH), and Accrual to Clinical Trials (ACT) Network.

Recruitment

Assistance with recruitment planning, resources, materials, and templates; cohort identification using self-service feasibility tools; ResearchMatch and StudyFinder; and recruitment in the Clinics and Surgery Center (CSC).

Regulatory support

Regulatory support for assistance with IND and IDE applications to the FDA, clinical trial monitoring, and navigating ClinicalTrials.gov.

Start-up guidance

Support for navigating the study start-up process, including feasibility reviews, protocol development support, multisite study planning, and more.

Thank You!

SPRINT Ambulatory BP Ancillary Study

- Objective: evaluate whether an intensive clinic (vs standard) based BP target resulted in lower:
  - Nighttime SBP (primary outcome)
  - Secondary outcomes
    - Daytime SBP
    - 24 hour SBP
    - Night/day SBP ratio (dipping)
    - SBP variability

SPRINT Ambulatory BP Ancillary Study Methods

- Ambulatory BP measured within 3 weeks of the 27M study visit at 15 SPRINT sites
- Ambulatory BP Monitoring
  - Spacelabs 90207
  - Non-dominant arm
  - Recorded BP every 30 minutes
  - Acceptable recording
    - ≥ 14 daytime readings (6AM to 12 midnight)
    - ≥ 6 nighttime readings (12 midnight to 6AM)
- Recorded time of day participants took antihypertensive medications
- Clinic BP measured using standard protocols

Ambulatory BP Participants
Baseline characteristics

	Intensive-treatment N=453	Standard-treatment N=444
Age	71.5 ± 9.3	71.5 ± 9.7
Female sex	132 (29.1)	125 (28.2)
Race/Ethnicity		
White	300 (66.2)	304 (68.5)
Black	127 (28.0)	124 (27.9)
Hispanic	13 (2.9)	8 (1.8)
Other	13 (2.9)	8 (1.8)
eGFR (ml/min/1.73 m^2, 24M)	67.3 ± 20.2	73.4 ± 21.1
Urine albumin/Cr (mg/g, 24M)	7.9 (4.9 to 15.2)	10.6 (6.1 to 28.4)

Difference in clinic and ambulatory BP (Standard – Intensive)

Variable	Primary Analysis		Secondary Analysis	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
27 month clinic systolic BP	15.95 (14.1, 17.8)	<0.001	16.35 (14.5, 18.2)	<0.001
Nighttime systolic BP	9.59 (7.7, 11.5)	<0.001	9.77 (7.8, 11.7)	<0.001
Daytime systolic BP	12.26 (10.6, 13.9)	<0.001	12.12 (10.4, 13.8)	<0.001
24 hour systolic BP	11.21 (9.7, 12.8)	<0.001	11.18 (9.6, 12.8)	<0.001

1. Primary analyses only adjust for clinic site.
2. Secondary analyses also adjust for age, sex, race/ethnicity, eGFR, smoking status, and alcohol use. Nighttime systolic BP also adjusted for nighttime dosing of antihypertensive medications (between 6pm and 2am), while daytime systolic BP was also adjusted for dosing of antihypertensive medications between 4am and 10am. All other ABPM measures were adjusted for antihypertensive medication use between 6pm and 2am and/or between 4am and 10am.

Clinic and Ambulatory BPs

	Intensive-treatment Mean ± SD	Standard-treatment Mean ± SD	Standard – Intensive Difference (95% CI)
Baseline in-clinic systolic BP	136.4 ± 15.4	138.0 ± 14.8	1.7 (-0.3, 3.6)
27M in-clinic systolic BP	119.7 ± 12.8	135.5 ± 13.8	15.8 (14.0, 17.6)
Nighttime systolic BP	115.7 ± 14.6	125.5 ± 14.6	9.8 (7.9, 11.7)
Daytime systolic BP	126.5 ± 12.3	138.8 ± 12.6	12.3 (10.6, 13.9)
24 hour systolic BP	122.7 ± 12.0	134.0 ± 11.8	11.3 (9.7, 12.8)

SPRINT ABPM – Start up

- Startup
  - Provided draft IRB language including consent form
  - UMN team assisted with local IRB submissions
  - Multiple zoom calls
  - Critical to talk directly with individual who will be doing the work
  - Critical that the individual doing the work has the MOP
- Keeping sites engaged
  - Payments were per subject enrolled
  - Quarterly meetings to track progress

Questions?

Hockey4hypertension.org