Agenda

• Background – J Schmelz, B Weaver
• Expanded Services – J Bates
• New Process – P Miranda
• New Forms – B Otten, M Baghezza
• SOM Clinical Research Support - C. Peebles
Background
Time to First Subject Enrolled
In early 2017, the VPR’s office began working to identify ways to evaluate and improve how clinical trials are initiated at the Health Science Center, and the approval processes required up to the time the first subject is enrolled. These efforts cross multiple departments - VPR, CTO, OSP, IRB, FORU etc. as well as affiliate institutions such as UHS and VA, and have been the focus of a larger working group for almost a year. It is our goal to centralize and improve the clinical trial study initiation and approval process, using a collaborative team effort (the Lean Six Sigma approach). To do so, a diverse working group was formed. In order to get a broad picture of everything required to get a study approved and a subject enrolled, the working group was comprised of designees from affiliate research offices, institutional and clinical departments, and research team members. Together they reviewed forms, definitions, data fields, fee schedules and looked at everything from sponsor inquiries, to feasibility, budgets, clinical trial agreements, IRB submissions and study staff and recruitment plans. Their work has culminated in outlining a comprehensive approval process that will help take multiple submission, analysis and review processes down to one clinical trial initiation process.
Working Group

• Kathryn Altman – SON/Health Professions
• Rachelle Jonas – Research Coordinator
• Jason Bates – VPR/CTO
• Deborah Mote – CTSA/IIMS
• Tiffany Mince – UHS Research
• Brandie Otten – VPR/OCR
• John Roache – CTSA/IIMS
• Amy Saklad – Research Coordinator
• Can Saygin – CTSA/IIMS
• Rachel Schofield - OSP

• Joseph Schmelz - VPR
• Susanne Schmidt – CTSA/IIMS
• Aubree Shay – CTSA/IIMS
• Kim Summers – VPR/RRP
• Anna Taranova – UHS Research
• Robin Tragus – Research Coordinator
• Michelle Trimble - VA
• Brandi Weaver – Research Coordinator
• Deidre Winnier – UHS Research
• Melanie Zuniga-Rapp – VPR/COI
NIH Definition of a Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

An "intervention" is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.

Examples include: drugs/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies. (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
<table>
<thead>
<tr>
<th>Field Label</th>
<th>Field Type</th>
<th>Field Definition</th>
<th>Initial Request and PI Identified</th>
<th>Targeting</th>
<th>Contract Negotiation</th>
<th>Initiate Budget Negotiation</th>
<th>Inst Services Budget Dev - CRU</th>
<th>Inst Services Budget Dev - UHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Initial request to initiate CT</td>
<td>Date</td>
<td>Date HCC receives sponsor query</td>
<td>Input</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory Sponsor Information</td>
<td>Text</td>
<td>The agency, organization, company or person primarily responsible for initiating and overseeing the research and ensuring the study complies with federal regulations.</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
</tr>
<tr>
<td>Financial Sponsor(s) information</td>
<td>Text</td>
<td>The agency, organization, company, or person that pays for the trial</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
</tr>
<tr>
<td>CRO information</td>
<td>Text</td>
<td>An organization that provides support to the pharmaceutical, biotechnology, medical device industries, or other sponsors in the form of research services purchased on a contract.</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
</tr>
<tr>
<td>Network information</td>
<td>Text</td>
<td>A group of institutions or organizations that are affiliated with each other in order to collaborate on multi-center clinical trials.</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
</tr>
<tr>
<td>Cancer related?</td>
<td>Single Select</td>
<td>Any clinical research protocol involving cancer topics</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
</tr>
<tr>
<td>Primary Therapeutic Area</td>
<td>Single Select</td>
<td>The therapeutic focus being studied.</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
<td>Input</td>
</tr>
<tr>
<td>Working Title</td>
<td>Text</td>
<td>A short or temporary title created by the site.</td>
<td>Output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of CTO Navigator assigned</td>
<td>Text</td>
<td>A CTO staff member assigned the responsibility for coordinating start-up activities for a specific study</td>
<td>Output</td>
<td>Input</td>
<td>input</td>
<td>input</td>
<td>input</td>
<td>input</td>
</tr>
<tr>
<td>Date CTO Navigator assigned</td>
<td>Date</td>
<td></td>
<td>Output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of potential Site PI's contacted</td>
<td>Text</td>
<td>Site PI is the individual with primary responsibility for the research activities at a specific engaged institution. There should be only one Site PI for each study site. An individual can serve as both a Study PI and Site PI, or can serve as the Site PI at more than one site.</td>
<td>Output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start Date PI Search</td>
<td>Date</td>
<td>Date search for potential Site PIs</td>
<td>Output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VPR CTO Expansion Plan

“Enhance the clinical trials infrastructure”

is a research strategy in the Health Science Center's Strategic Plan

Goals:
• reduce administrative burden on clinical trialists,
• negotiate budgets that are better aligned with actual costs,
• increase efficiency & effectiveness:
  • Shorter time to study initiation
  • Improved budget margins and F&A recovery
  • Continued compliance with the ever-changing regulatory landscape
Expanded Services

Centralized support for clinical trials
Timeline – CTO Expanded Services

- **February 2018**
  - Phase 1 – Support for **NEW** Clinical Trials
  - Coordinate start-up activities for all new “industry sponsored” trials
  - Provide budget review service for all new grant applications

- **2019**
  - Phase 2 – Support for all **On-Going** Clinical Trials (Legacy and New)
  - Coordinate modification of budgets/contracts
CTO Expanded Services

**CURRENT**
- Billing Risk Assessment
- Research Coverage Analysis
- Management of Participant Payments
- Study build and training for Velos eResearch (CTMS - Clinical Trial Management System)

**EXPANDED**
- Initial feasibility assessment, preliminary communication with sponsor
- Coordinate CDAs & CTAs with OSP
- Price quotes from service providers
- Budget development and negotiation with sponsor
- Invoice and collect initial start-up fees from sponsor
Early Notification

**Pre-Development Research Navigator Project**
- CTO Notified of Sponsor/CRO outreach:
  - Sponsor/CRO outreach looking for interested investigators
  - Local Investigator has been contacted directly by a Sponsor/CRO
  - Trial Planning Phase; early on, study idea or concept only
  - Limited study information

**Development Site Selected, Contract & Budget Process**
- Sponsor has Selected our Site
- Final Protocol
- Clinical Trial Agreement
- Budget

Clinical Trial Portal
Goals of CTO Expanded Services

Reduce Administrative Burden, Increase Efficiency and Effectiveness through Centralized processes.

Coverage Analysis
- Procedures & CPT Codes
- Quantity
- Coverage Determination
- Location of Service

Participant Payment Plan
- Inst B

Budget
- Align budgets with actual costs
- Improved budget margins and F&A Recovery
- Including Price Requests

All completed prior to submission to the IRB!
CTO Expanded Services

CTO works with OSP and Study Team to Finalize CTA & Budget preparing for IRB submission
New Process

New project planning assistance.
CTO is the new “Front Door”

• Initial notification using the “Portal”
• What happens next?
• What CTO will do
• What study team will do
Clinical Trials Office

Roadmap on our Webpage

Clinical Trial Roadmap

Web Portal Front Door

Clinical Trial Submission Portal
Start-up Process

Study team and CTO collaborate to reach Site Selection

CTO works with OSP and Study Team to Finalize CTA & Budget preparing for IRB submission
Pre-Development

Research Navigator Project

• CTO Notified of Sponsor/CRO outreach:
  • Sponsor/CRO outreach looking for interested investigators
  • Local Investigator has been contacted directly by a Sponsor/CRO
  • Trial Planning Phase; early on, study idea or concept only
  • Limited study information
Development

Site Selected, Contract & Budget Process
  • Final Protocol
  • Clinical Trial Agreement
  • Budget
Study Team Responsibilities

• Responsibilities Include:
  • Determining Locations where research will be performed
  • Coordinating the Study Team members
    • Study Team training
  • Submission of Institutional Research Application Form
    • IRB and Institutional Approvals
  • Conducting the Study & Patient Recruitment
CTO Clearance for IRB Submission

- Final Budget
- Final Coverage Analysis
- Participant Payment Plan
- IRB & Institutional Forms
New IRB & Institutional Approval Process and Form

Reduce duplication by using project planning documents.
<table>
<thead>
<tr>
<th>Required Forms for Initial Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Institutional Research Application</strong></td>
</tr>
<tr>
<td>*Required Note: If this study is a clinical trial, do not download/complete this form. Complete and submit the Institutional Clinical Trial Research Application received from the CTO office instead.</td>
</tr>
<tr>
<td><strong>Inst M - Personnel Form</strong></td>
</tr>
<tr>
<td>*Required</td>
</tr>
<tr>
<td><strong>UTHSCSA IRB Application</strong></td>
</tr>
<tr>
<td>*Required</td>
</tr>
<tr>
<td><strong>Form BB - Sponsor's protocol OR</strong></td>
</tr>
<tr>
<td>*Required Include the sponsor's protocol with your submission OR</td>
</tr>
<tr>
<td><strong>Form BC - Protocol Template Form</strong></td>
</tr>
<tr>
<td>Use the Form BC template if you do not have a sponsor's protocol.</td>
</tr>
<tr>
<td><strong>Form A - Signature Assurance Sheet</strong></td>
</tr>
<tr>
<td>*Required How to digitally sign Adobe forms.</td>
</tr>
</tbody>
</table>
### Item 6: Coding Plan

<table>
<thead>
<tr>
<th>Description</th>
<th>Code</th>
<th>Algorithm</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable, no identifiable information will be collected (Y)</td>
<td>(Y)</td>
<td>(Y)</td>
<td>(Y)</td>
</tr>
</tbody>
</table>

**Note:** The code, algorithm, or probability should not be derived from other related information about the individual, and the means of re-identification should only be known by authorized parties and not disclosed to anyone without the authority to identify, access, describe, or collect it.

**Describe the method that will be used to create and assign a unique study code to the data:**

- **Electronic**
- **Paper**
- **Other**

**Describe the method that will be used to create and assign a unique study code to the specimens:**

- **Electronic**
- **Paper**
- **Other**

**What is the format of the key:**

- **Electronic**
- **Paper**
- **Other**

**Who will have access to the key:**

- **Local**
- **Remote**
- **Other**

**Where will the key be stored and how will it be protected:**

- **Local**
- **Remote**
- **Other**

**Describe confidentiality measures:**

- **Electronic**
- **Paper**
- **Other**

### Item 7: Data / Specimen Storage Plan

<table>
<thead>
<tr>
<th>Data / Specimen Storage Plan</th>
<th>Code</th>
<th>Algorithm</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable, no identifiable information will be collected (Y)</td>
<td>(Y)</td>
<td>(Y)</td>
<td>(Y)</td>
</tr>
</tbody>
</table>

**Check off and complete the table as applicable:**

- **Electronic**
- **Paper**
- **Other**

**Describe the method that will be used to store data:**

- **Electronic**
- **Paper**
- **Other**

**Describe the method that will be used to store specimens:**

- **Electronic**
- **Paper**
- **Other**

**Describe the method that will be used to store sensitive data:**

- **Electronic**
- **Paper**
- **Other**

### Item 8: Calculating HIPAA Disclosure

**Covered Entity where the source PHI is held (Source Location):**

- **Paper files**
- **Electronic files**

**Research Storage Location(s):**

- **Paper files**
- **Electronic files**

**Where do you plan to store the PHI from this organization?**

- **Local**
- **Remote**
- **Other**

**If applicable, list the names of other organizations that will be receiving PHI:**

- **Electronic**
- **Paper**
- **Other**

**Describe the method that will be used to transfer PHI from one location to another:**

- **Electronic**
- **Paper**
- **Other**

**Describe the method that will be used to transfer PHI from one organization to another:**

- **Electronic**
- **Paper**
- **Other**

### Item 9: Maintaining Confidentiality

**Not applicable, no identifiable information will be viewed (Y) (looked at):**

- **Electronic**
- **Paper**
- **Other**

**Describe measures that the research team will take to protect the confidentiality of subjects while viewing private information:**

- **Electronic**
- **Paper**
- **Other**

**Other:**

- **Describe different approach:**

### Item 10: Sharing of Research Data / Specimens to Entities Outside the Affiliated Study Sites

**Not applicable, not sharing data / specimens with groups outside of the HIPAA rule of study sites:**

- **Electronic**
- **Paper**
- **Other**

**Describe how the materials will be transferred from one location to another:**

- **Electronic**
- **Paper**
- **Other**

**Describe how the materials will be transferred from one organization to another:**

- **Electronic**
- **Paper**
- **Other**

**Describe how the materials will be transferred from one location to another:**

- **Electronic**
- **Paper**
- **Other**
Exempt / Chart Review – skip to last two questions
<table>
<thead>
<tr>
<th>Item 29: Other drugs or devices</th>
<th>Only2</th>
<th>Intervention performed (e.g. UT, INJ, STING)</th>
<th>Intervention performed (e.g. UT, INJ, STING)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Item 39: Imaging              |       |                                            |                                            |
| Picture-taking procedures     |       |                                            |                                            |
|                               |       |                                            |                                            |

| Item 38: Imaging              |       |                                            |                                            |
| Who is performing the procedure? (select applicable) |       |                                            |                                            |
| Research Team List Institution(s) where procedure performed (e.g. UT, INJ, STING) |       |                                            |                                            |
| Non-Research Team Study Site Employees List institutions where procedure performed (e.g. UT, INJ, STING) |       |                                            |                                            |
| Outside Source                |       |                                            |                                            |

| Item 29: All Other Research Activities |       |                                            |                                            |
| Activities, Procedures, Surveys, Charts, Questionnaires, etc. |       |                                            |                                            |
| Who is performing the activity/service? (select applicable) |       |                                            |                                            |
| Research Team List Institution(s) where activity performed (e.g. UT, INJ, STING) |       |                                            |                                            |
| Non-Research Team Study Site Employees List institutions where activity performed (e.g. UT, INJ, STING) |       |                                            |                                            |
| Outside Source                |       |                                            |                                            |
## Item 30: Research Team - Roles and Activities

Not applicable — this is an exempt protocol or chart review study.

### Column A

**Build your research team below by identifying key position titles.**

At a minimum, all full-time clinical investigators must be included. Other supported positions have been inserted below. Delete positions as appropriate to your study.

**Position Title (Do NOT modify position titles)**

### Column B

**For each key position, list the roles & responsibilities that could be assigned to research team members in this position. Use the following codes to identify the responsibilities that are applicable for the role you created in Column A, but all responsibilities apply to every study.**

<table>
<thead>
<tr>
<th>General responsibilities</th>
<th>Oversight responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. recruitment</td>
<td>18. recruiting the research team members and assessing compliance with study protocol</td>
</tr>
<tr>
<td>2. assess inclusion and exclusion criteria</td>
<td>19. lead or direct the study site(s) at other locations</td>
</tr>
<tr>
<td>3. obtain informed consent</td>
<td>20. determine significance of subject safety indicators (e.g., AE/GBS, UDS, SUGAR, UPS, etc.)</td>
</tr>
<tr>
<td>4. assist with the consent process</td>
<td>21. determine the significance of protocol deviations or violations</td>
</tr>
<tr>
<td>5. source documentation or case report form completion</td>
<td>22. ensure the integrity of the data</td>
</tr>
<tr>
<td>6. perform physical examination</td>
<td>23. sponsor investigator monitoring and reporting</td>
</tr>
<tr>
<td>7. perform physical assessment</td>
<td>24. other</td>
</tr>
<tr>
<td>8. obtain medical history or evaluate concomitant medications</td>
<td>25. other</td>
</tr>
<tr>
<td>9. prescribe intervention being tested</td>
<td>26. other</td>
</tr>
<tr>
<td>10. administer intervention being tested</td>
<td>27. other</td>
</tr>
<tr>
<td>11. perform study procedures</td>
<td>28. other</td>
</tr>
<tr>
<td>12. adverse event inquiry and reporting</td>
<td><strong>“Requires CIT Training”</strong> Safety, Hemostatic, Infectious Substances, Clinical Specimen, and Dry Ice</td>
</tr>
<tr>
<td>13. laboratory or other specimen handling</td>
<td><strong>“Requires CIT Training”</strong> Safety, Hemostatic, Infectious Substances, Clinical Specimen, and Dry Ice</td>
</tr>
<tr>
<td>14. other specimen shipping</td>
<td><strong>“Requires CIT Training”</strong> Safety, Hemostatic, Infectious Substances, Clinical Specimen, and Dry Ice</td>
</tr>
<tr>
<td>15. investigational product dispensing &amp; accountability</td>
<td><strong>“Requires CIT Training”</strong> Safety, Hemostatic, Infectious Substances, Clinical Specimen, and Dry Ice</td>
</tr>
<tr>
<td>16. regulatory &amp; essential documents, other record keeping or admin function</td>
<td><strong>“Requires CIT Training”</strong> Safety, Hemostatic, Infectious Substances, Clinical Specimen, and Dry Ice</td>
</tr>
<tr>
<td>17. review private identifiable information</td>
<td><strong>“Requires CIT Training”</strong> Safety, Hemostatic, Infectious Substances, Clinical Specimen, and Dry Ice</td>
</tr>
</tbody>
</table>

### Column C

**For each position, list the minimum credentials & training required for any person assigned to this role. Use the following codes to identify the credentials & training for the role you created in column A.**

A. Medical license (US)
B. Dental license (US)
C. RN license (US)
D.輻射線技士 (US)
E. **license (US)**
F. Good Clinical Practice (GCP) training
G. Research related certification (e.g., CISSP)
H. Advanced academic degree
I. Sponsor certification
J. **certification**
K. **certification**
L. Other:
M. Other:

Training and Scope of Practice requirements:
http://research.chla.edu/docs/training.shtml
Submission Changes for Clinical Trials

Clinical Trials Process:

1) PI submits through CTO Portal
2) PI receives email clearance and Clinical Trial Research Application Form from CTO
3) PI downloads and completes all other study applicable forms
4) Submits Clinical Trial Research Application instead of the Institutional Research Application Form along with other applicable study forms to IRBM@uthscsa.edu
Submission Changes – Non Clinical Trials

1. This study is a Clinical Trial. Go to CTO Portal and work with CTO staff.

2. Not a Clinical Trial. Go to IRB website and download forms for new study. Submit to IRB.
Scheduling Submissions for IRB Review

• **February 1, 2018** all clinical trials will be required to utilize the new submission process

• Submissions are scheduled for the next IRB meeting once:
  1. CTO Clearance has been obtained,
  2. Remaining forms have been submitted to the IRB, and
  3. The study is "Board Ready."
Help with IRB Submission Process

Research Concierge Service

Offering Regulatory Guidance and Assistance for Research Staff
Introducing the Clinical Trials Office to Assist with Participant Payments, Billing Risk Review and Velos at no charge!

Representatives from IRB, IACP, OCR and CTO are eager to assist you.

Upcoming Dates

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2, 2018</td>
<td>1pm-4pm</td>
</tr>
<tr>
<td>Jan 3, 2018</td>
<td>9am-12pm</td>
</tr>
<tr>
<td>Jan 17, 2018</td>
<td>9am-12pm</td>
</tr>
<tr>
<td>Jan 31, 2018</td>
<td>9am-12pm</td>
</tr>
</tbody>
</table>

Location of Concierge:
Main Campus (Long Campus)
Library, 2nd Floor Computer Classroom, Room 2011
SOM Research

Courtney Peebles, MPH
Senior Research Coordinator
peeblesc@uthscsa.edu
FY18 mission: 1) Increase basic science department funding by 5% ($3M) and 2) Continue to set stage for clinical research growth

**G1. Research environment**
Promote a culture that values research and research faculty

**G2. Embrace Excellence**
Use metrics to review performance; align investment with our strategic priorities; invest in productive faculty

**G3. Faculty**
Recruit top tier candidates, and develop and retain cadre of talented investigators

**G4. Increase extramural funding**
Provide support for faculty to engage in research and obtain extramural funding
Goal One. Research environment
Promote a culture that values research and research faculty

Activities

Structural Change Initiatives
• Task Force on Philanthropy
• Task Force on Research Operations

Faculty Engagement Activities
• Faculty Research Socials and Chalk Talks
• Accolades newsletter

Student Programs
• Research Connect

SOM Faculty Research Socials
Date: 2nd Thursday of every month
Time: 5pm-6pm
Place: ALTC 205

Close out the day in the company of fellow researchers with wine, cheese, non-alcoholic drinks, and appetizers.
Goal Two. Embrace Excellence

Use metrics to review performance; align investment with our strategic priorities; invest in productive faculty

Activities

Pilot Funding Programs

- Harmonizing programs across the SOM to maximize benefit to faculty
- Basic and Clinical Science Pilot Program- traditional pilot program
- Clinical Investigator Kickstart Program- can fund planning activities necessary for team development and infrastructure building in addition to traditional pilot proposals

Clinical Faculty productivity evaluation

- Piloting metrics
Goal Three. Faculty
Recruit top tier candidates, and develop and retain cadre of talented investigators

Activities

Bridge Funding Program
- Provides up to 12 months of support to faculty with an established track record of obtaining extramural funding experiencing a *temporary* disruption of funding.
- Quarterly submission (15th of February, May, August, November)

Faculty Research Awards
- Distinguished Researcher Award
- Research Mentor Award

Special Advisor to the Dean for Research Faculty Development
Goal Four. Increase Extramural Funding

Provide support for faculty to engage in research and obtain extramural funding

Activities

Clinical Research

- Clinical Scholars Academy *coming soon*
- Grants 101/102
- Increase opportunities for partnership formation between clinical and basic science faculty

Research and Grant Support

- McAllister & Quinn
- Research Affinity Teams (RAffTs)
  - Visionaries Pilot Award
- Limited Submissions
- Resources and Environment Sample Language
G4. Increase Extramural Funding

McAllister & Quinn

Grant writing and project management assistance

Training opportunities

- NIH
- DoD
  - CDMRP webinar in February 2018

Mapping our research capacities to federal funding priorities
G4. Increase Extramural Funding

Provide support for faculty to engage in research and obtain extramural funding

- Create a culture of research in clinical departments
- Create a pipeline for research
- Increase number of grants submitted
Questions and Discussion