Integrating Imaging Criteria Into Trial Endpoints

Gregory Goldmacher, MD, PhD, MBA
Sr. Director, Translational Biomarkers
Merck Research Laboratories

CBI Imaging In Clinical Trials
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Preview

- Purpose and structure of criteria
- Choosing and using oncology criteria
- Combining imaging and clinical data
- Reducing image variability
- Training sites
Purpose and Structure of Imaging Criteria
What Is An Endpoint?

- Measurement
- Determines whether trial met its objective

Objective

Endpoint
What Kind Of Measurement?

• Direct measurement
  – BP, LDL

• Derived value
  – PFS, PRO score

• Event ("clinical endpoint") → event rate
  – Objective response, cardiac death
What Can Be Measured

- Survival
- Symptoms
- Disease severity - biomarkers
  - Physiological, molecular, cellular, imaging

- Cardiovascular
  - Vessel stenosis

- Cancer
  - Tumor size

- Arthritis
  - Joint changes

- CNS
  - MS lesions
Common Oncology Endpoints

- OS – Overall survival
- PFS – Progression-free survival
  - DFS – Disease-free survival
- ORR – Objective response rate
  - DOR – Duration of response
- DCR – Disease control rate
- Symptoms/Quality of Life (QLQ-30, EQ-5D, etc.)
Why Use Response Criteria?

**Key goal:**
Track change in tumor burden over time

**High priority:**
Minimize variability
Sources of Variability

Different or poor scans

Manual QC

Response Criteria

Variability

Different interpretations

Result
Response Criteria

Criteria are rules about
- What and how to quantify
- Categories and thresholds (e.g. PR = 30% ↓)
- Lesions → Visits → Endpoints
- How to integrate clinical data
- Special situations

Baseline
- Lesions
  - Quantitative
  - Qualitative

Treat

Visit 1
- Lesion changes
  - Visit 1 response
  - Visit 1 response

Treat

Visit 2
- Lesion changes
  - Visit 2 response
  - Visit 2 response

Endpoints
- Date of progression → PFS
- Best response → ORR
- etc…
Choosing and Using Criteria
A Few Commonly Used Criteria

- Solid tumors – RECIST
  - Modified RECIST – HCC, mesothelioma
- Lymphoma – Cheson 2007, Lugano
  - Other heme – Hallek (CLL), IMWG (MM)
- Glioblastoma – Macdonald → RANO
- Prostate – PCWG2 and 3

- irRC → irRECIST (multiple approaches) → iRECIST 2017
## Older vs Newer

### Pros of Older
- Regulatory familiarity
- Comparability to older trials
- Implementation experience

### Pros of Newer
- Incorporate latest techniques
- Expert insight
- Clarifications

### Example: lymphoma
- 1999 → 2007 → 2014

### Bottom line:
- Primary EP – established criteria
- Exploratory EP – newer variants
Modifications

• Modifications and fusions are common
  – Example: # target lesions
  – Example: PCWG + RECIST 1.1

• Consider functional need
  – Example: HCC
    • Modified vs traditional RECIST varies by drug MOA

• Get regulatory buy-in
  – Example: Mesothelioma
Who Performs Assessment

• Site assessment: keep it simple
  – 1 set of criteria
  – Consider what will stop treatment
    • Example: RECIST vs. irRECIST

• Central review: try out multiple criteria
  – Be clear on order of priorities
  – Control costs
Early – Novel Imaging Biomarkers

- **Macro Size**
  - Linear → Volume

- **Micro Structure**
  - CT: Density/Texture
  - MRI: DWI

- **Vascularity**
  - CT/MR Perfusion
  - DCE-MRI

- **Metabolism**
  - PET: FDG, FLT

- **Other Signatures Kinetics**
Early – Novel Imaging Biomarkers

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Graph: Volume vs. Time

Tx → Increase in Volume
Reducing Image Variability
Assess Sites Before Trial

- Establish trial needs
- Find out imaging capabilities - qualification
  - iCRO or sponsor
  - Existing networks (e.g. ACR, SNM)
- Get local radiologists involved, if possible
During Start-up

• Imaging manual
• Training for site
  – Get rad tech involved if at all possible
• Test scan usually not needed in late phase
• Reliable contact with site radiology department
During Trial

- Real time QC and feedback - iCRO

- Clear guidelines for QC team
  - What to query
  - What is flexible vs what is a must

- Participation of site radiologist
  - Improves image quality and site reads
What Scans To Get

• Typical oncology trial: chest, abdomen, pelvis
  – + protocol-specific: neck, brain, bone scan
  – Define off-protocol and unscheduled imaging

• Optional anatomy – define lesions as non-target
  – If missed on later scan, can still have a response
Combining Imaging And Clinical Data
Role Varies

- Solid tumors – typically minimal clinical data
- “Special” tumors – significant clinical component
- Hematological cancers – wide range
RECIST

Baseline

Lesions

Target

Non-target

Treat

Visit 1

Target

Non-target

New

Visit

CR, PR, SD, PD

CR, NN, PD

Yes, No

PR

Visit

Visit 2

Target

Non-target

New

Visit

CR

CR

No

Tumor Markers
RANO

Baseline

Lesions

Target

Non-target

Treat

Visit 1

Target

CR, PR, SD, PD

Non-target

CR, SD, PD

New

Yes, No

Treat

Visit 2

Visit MRI

CR, PR, SD, PD

Steroids

Off, stable, increased

Neuro

Stable/impr, worsened

Final
## Hallek CLL (2008)

<table>
<thead>
<tr>
<th>Group</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodes</strong></td>
<td>None &gt;1.5 cm</td>
<td>Decrease ≥50%</td>
<td>-49+ to + 49%</td>
<td>Increase ≥50%</td>
</tr>
<tr>
<td></td>
<td>Normal size</td>
<td>Decrease ≥50%</td>
<td>-49+ to + 49%</td>
<td>Increase ≥50%</td>
</tr>
<tr>
<td></td>
<td>Normocellular</td>
<td>≥30% lymph Nodules</td>
<td>No change</td>
<td>Increase lymph to &gt;30% from normal</td>
</tr>
<tr>
<td></td>
<td>&lt;30% lymph no nodules</td>
<td>Not done</td>
<td></td>
<td>Increase ≥50%</td>
</tr>
</tbody>
</table>

| **Liver/spleen** | Normal size | Decrease ≥50% | -49+ to + 49% | Increase ≥50% |
| | Increase ≥50% | | | |

| **Marrow** | Normocellular | ≥30% lymph Nodules | No change | Increase ≥50% |
| | <30% lymph no nodules | Not done | | |

| **Clonal B cells** | < 4000/μL | Decrease ≥50% | -49+ to + 49% | Increase ≥50% |
| | > 4000/μL | Increase ≥50% | | |

| **Group B** | **Clinical** | **Platelets** | **Hemoglobin** | **PMNs** |
| | | >100,000/μL | >11 g/dL | >1500/μL |
| | | >100,000/μL | >11 g/dL | >1500/μL |
| | | >100,000/μL | >11 g/dL | >1500/μL |
| | | >100,000/μL | >11 g/dL | >1500/μL |

**Imaging**
- **≥ 2 ALL AND ≥ 1 ALL**
- **ANY**
- **ALL**
- **ANY**

**CLL** - Chronic Lymphocytic Leukemia
Site vs Central Assessment

• Site review – define process and trust clinician
  – Build logic checks into case report forms, if possible

• Central review
  – Define data to extract from site CRFs
  – Format and pathway: structured data file vs PDF
  – Decide central process
    • Radiologist – simple binary data
    • Oncologist or adjudication committee
Training Sites
Complementary Expertise Needed

Radiologist

Reads scans

Knows rules

Clinical Trialist
Delivery Channels

- Investigator meeting
  - Radiology attendance varies by geography
- Live teleconferences
- Recordings
- Written guides
- Tools (eg calculators)
  - Caution! – “medical device”
Content and Process

- Train on process issues
  - Example: improper de-identification
- Document training for regulatory compliance
- Vendor can handle site training

- Train internal staff
  - Monitoring, data management
- Expect turnover – train, rinse, repeat
Key Takeaways

• Choose criteria based on trial needs
• Keep protocol “high level”
  – Describe modifications
  – Get regulatory buy-in
• Engage imaging expertise early in trial planning
  – Internal group, consultant, or iCRO
• Train, train, train