# Control Arms for Future Clinical Trials

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# Historical Controls

- Became an acceptable type of control for trials of Interferon-free regimens since October 2011 Forum Meeting
- Note: some were actually early vs. delayed therapy in which patients were randomized to a regimen vs. placebo for the first 12-24 weeks.
- Was considered a “temporary” recommendation until a standard of care, interferon-free regimen was approved.
- Strongly believe this was the correct decision scientifically, but outside groups have criticized use of historical trials for basis of approval and have used this issue to cast doubt on efficacy/or even deny reimbursement.
- Controlled trials allow for direct safety comparison, perhaps less important for DAA vs INF-based because of the overwhelming profile of IFN but important for discriminating two DAAs

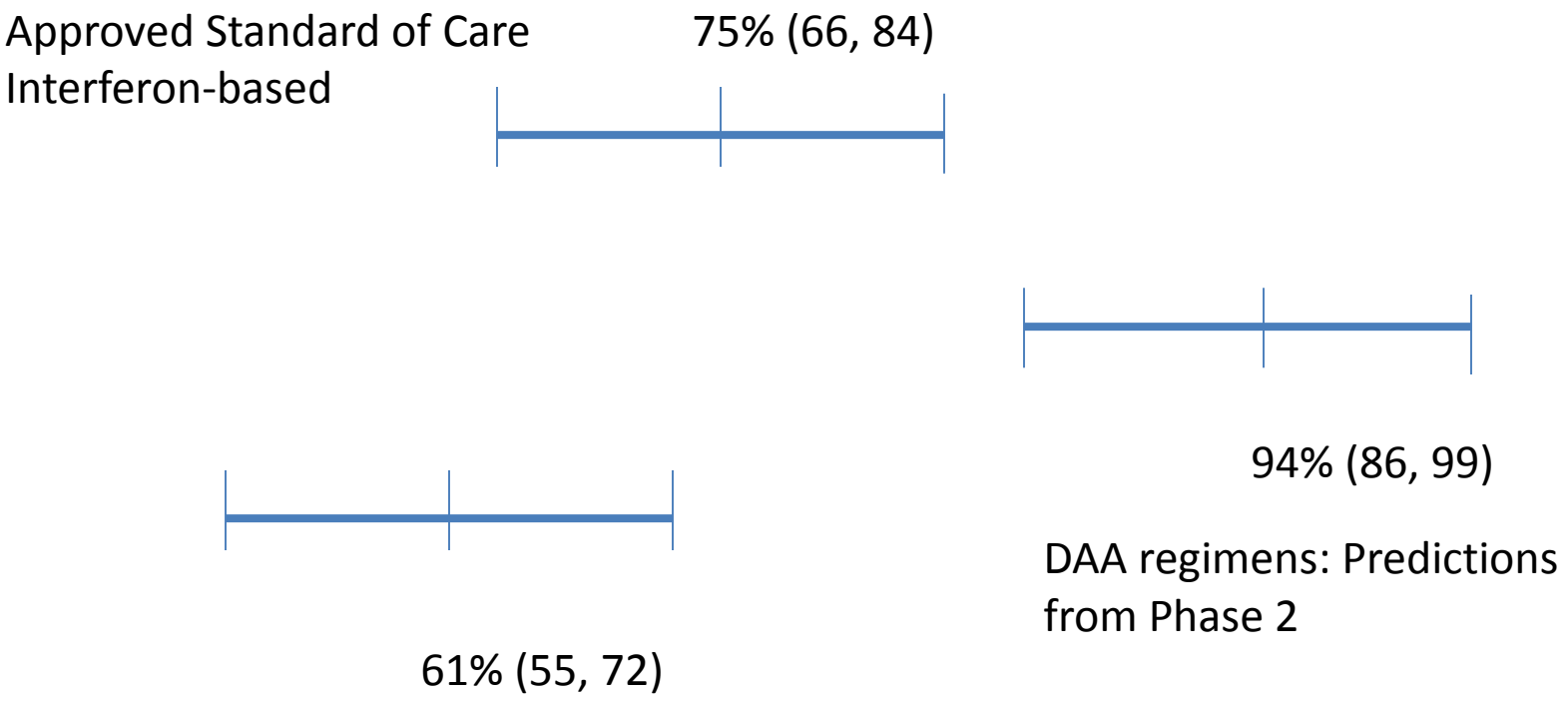
# Regulations (guidance) and Historical Controls

- CFR 314.126 lists historical controls under adequate and well controlled studies
- E10 Guidance; “In unusual cases, the course of illness is in fact predictable in a defined population and it may be possible to use a similar group of patients previously studied as a historical control”
- If the effect of the drug is self evident (anesthesia)
- Objective endpoint helpful (SVR)

# 2011: Historical Control Rationale

- For many patients with CHC there were no approved therapies
- Why subject participants to Interferon (and ribavirin) adverse reactions if not necessary?
- Phase 2 data of DAA regimens were already producing SVR rates beyond the upper confidence bound of SVR rates with IFN-based regimens.
- A regimen that was actually worse than approved IFN-based therapies would be clinically useful.

# 2011 Thinking (not today) Efficacy Obvious Enough (made choosing NI margin difficult)



# Possible Controls for New Trials

- Historical Control
- Active Control:  Best Approved Therapy
  - Will Change Over Time
- Current Possibilities:
  - Genotype 1a/1b: Sofosbuvir/Ledipasvir
  - Genotype 2/3: Sofosbuvir/ribavirin
  - Genotype 4-6:  No interferon-free controls

# Current Benchmarks

| Indication/Genotype | Regimen (Trial) | SVR |
|---|---|---|
| **Genotype 1**<br>Treatment Naïve with or without cirrhosis | SOF/LDV 12 weeks<br>(ION-3, ION-1) | 96-99% |
| **Genotype 1**<br>Treatment Experienced without cirrhosis | SOF/LDV 12 weeks<br>(ION-2) | 95% |
| **Genotype 1**<br>Treatment Experienced with cirrhosis | SOF/LDV 24 weeks<br>(ION-2) | 99% |
| **Genotype 2***<br>Overall | SOF/RBV 12 weeks<br>(POSITRON, VALENCE, FISSION) | 93-95% |
| **Genotype 3***<br>Overall | SOF/RBV 24 weeks<br>(VALENCE) | 84% |

*Response rates lower for subgroups: treatment-experienced, cirrhosis, combinations of factors

# Non-inferiority Trials Sample Size Estimates

(90% Power, Alpha 5%)

| Point Estimate (control/expected) | NI Margin = 6% (per arm/total) | NI Margin = 8% (per arm/total) |
|---|---|---|
| 93/93 | 310/620 | 175/350 |
| 95/95 | 227/554 | 128/256 |
| 96/96 | 183/366 | 103/206 |
| 97/97 | 139/278 | 78/156 |
| 98/98 | 94/188 | 53/106 |
| 99/99 | 48/96 | 27/54 |

# Superiority Trials—Sample Size Calculations (90% Power, Alpha 5%)

| Control Regimen Point Estimate | Expected Point Estimate Investigational | Per Arm/Total |
|---|---|---|
| 84%<br>*(Genotype 3: SOF/RBV)* | 90%<br>94% | 656/1312<br>201/402 |
| 94%<br>*(Genotype 2: SOF/RBV)* | 98%<br>99% | 500/1000<br>279/558 |
| 95%<br>*(Genotype 1 Treatment Exp.: SOF/LDV)* | 99% | 378/756 |

# Summary Comments

- Active Controlled Trials are preferred: more so for safety but may provide further discrimination of efficacy (sample size not prohibitive)
- More rigorous for treatment guideline and reimbursement decisions
- HIV Experience: as response rates improved, focus on preferred regimens that were robust across subgroups (HIV-RNA >100,000)
- Some room to improve with certain HCV subgroups
  - Cirrhosis
  - Treatment Experienced
  - Combinations of poor prognostic factors