Goal

Review the current landscape of recent clinical trials to examine the potential for a future natural history cohort comprised of the the placebo-arms of relevant clinical trials.

We reviewed clinicaltrials.gov looking for NASH/NAFLD trials registered as:

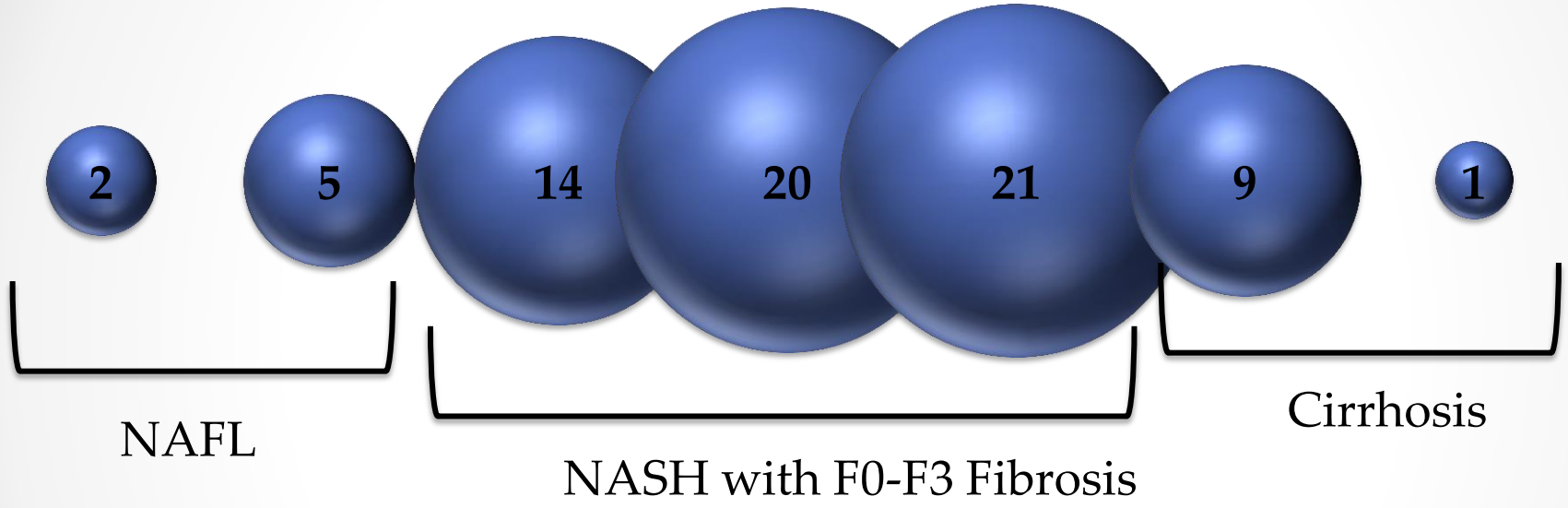
- Beginning since January 1, 2010
- Phase 2, 3, or 4
- Placebo-controlled
- Interventional trials studying drugs or biologicals on the regulatory pathway
- Investigating primary liver endpoints

25 clinical trials met these basic criteria

Review: Stages of Disease from Liver Forum #3

- Group 1: NAFL
  - 1 = Isolated Steatosis
  - 2 = Indeterminate NASH
- Group 2: NASH/F0-F3
  - 3 = Definite NASH without Fibrosis
  - 4 = NASH with early fibrosis
  - 5 = NASH with advanced fibrosis
- Group 3: Cirrhosis
  - 6 = NASH with compensated cirrhosis
  - 7 = NASH with decompensated cirrhosis

Number of Companies Studying each Phase of Disease



1 2 3 4 5 6 7

Stages of Non-Alcoholic Fatty Liver Disease

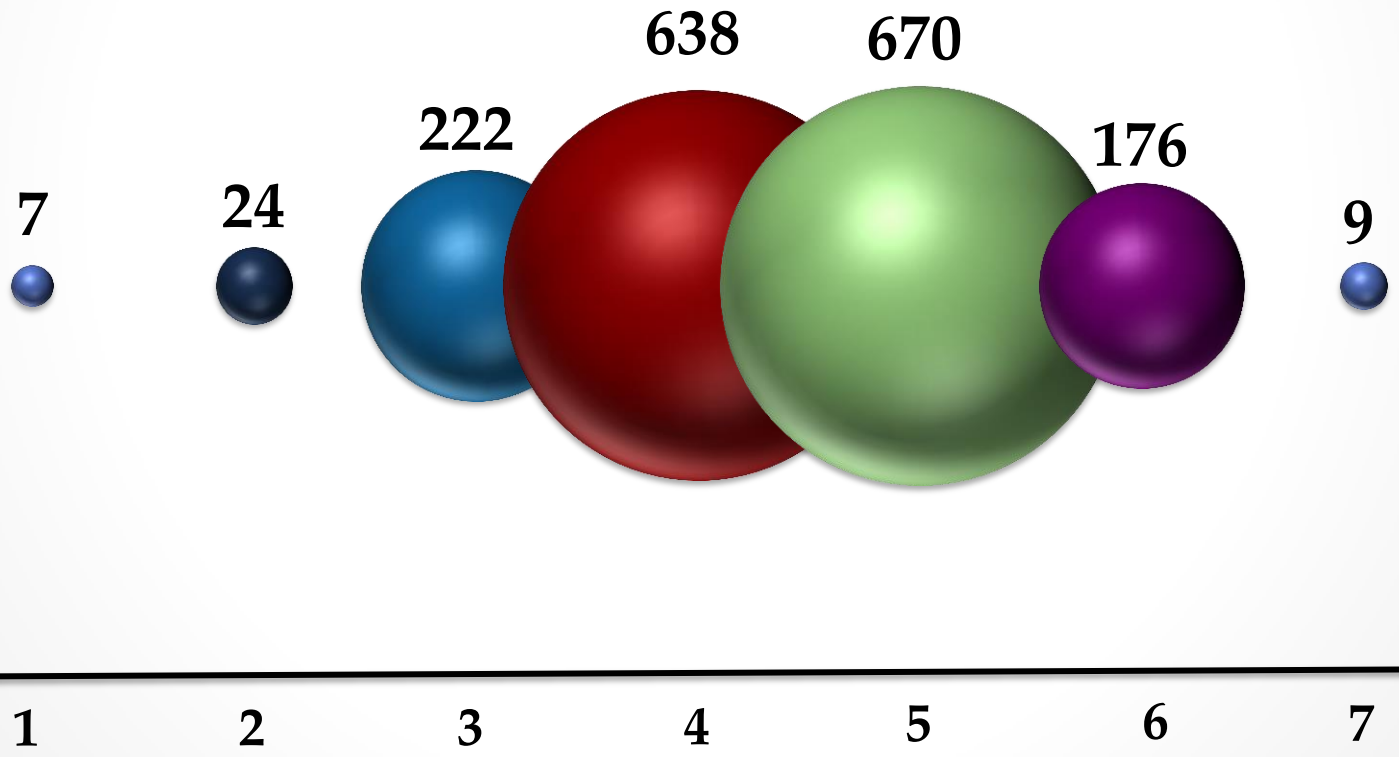
*Numbers don't add up to 25 because most studies are looking at more than 1 phase of disease

Estimate of Natural History Cohort

- The combined number of placebo arms from the 25 studies totals approximately 1760*

***Some studies didn't specify exact placebo group numbers placebo numbers were estimated off of total enrollment and number of study arms.**

Estimate of the Number of Placebo Participants in each Phase of Disease



*Numbers are estimated off of the estimated number of placebo patients in each study divided by the number of phases of disease that study enrolled.

The recent NASH/NAFLD clinical trials are

- # Trials conducting liver biopsy at baseline: 19/25
- # Trials conducting liver imaging at baseline: 6/25
- # Trials conducting imaging **or** biopsy at baseline: 2/25
- # of Trials looking at biologicals: 3/5
- # of Trials looking at drugs: 22/25
- Phases of trials:
  - Phase 2: 22
  - Phase 3: 2
  - Phase 4: 1

Placebo-cohort characteristics

- 7 of the 25 studies have publications available
  - In total, these 7 studies enrolled **404** placebo-arm participants
- We reviewed the publications to collect baseline characteristics of the placebo cohort from each of the individual trials.
- While there was some variability in the baseline characteristics that were collected and reported, many of the baseline data reported was consistently reported in all 7 studies (Table 1).

Table 1. Placebo-cohort baseline characteristics (n=404)

Baseline Characteristics	Weighted Average*
Age	50.7
Sex (% male)	39.9
ALT (U/L)	73.0
AST (U/L)	50.7
Alkaline Phosphatase (U/L)	78.5
Total Cholesterol (mmol/L)	4.8
LDL (mmol/L)	2.9
Triglycerides (mmol/L)	1.8

**Averages from each individual study were weighted based on placebo-arm sample sizes

Table 1. Placebo-cohort baseline characteristics (n=404) cont.

Baseline Characteristics	Weighted Average*
Fasting serum insulin (pmol/L)	154.2
Fasting serum glucose (mmol/L)	6.1
HOMA-IR	6.3
BMI (kg/m^2)	32.9

**Averages from each individual study were weighted based on placebo-arm sample sizes

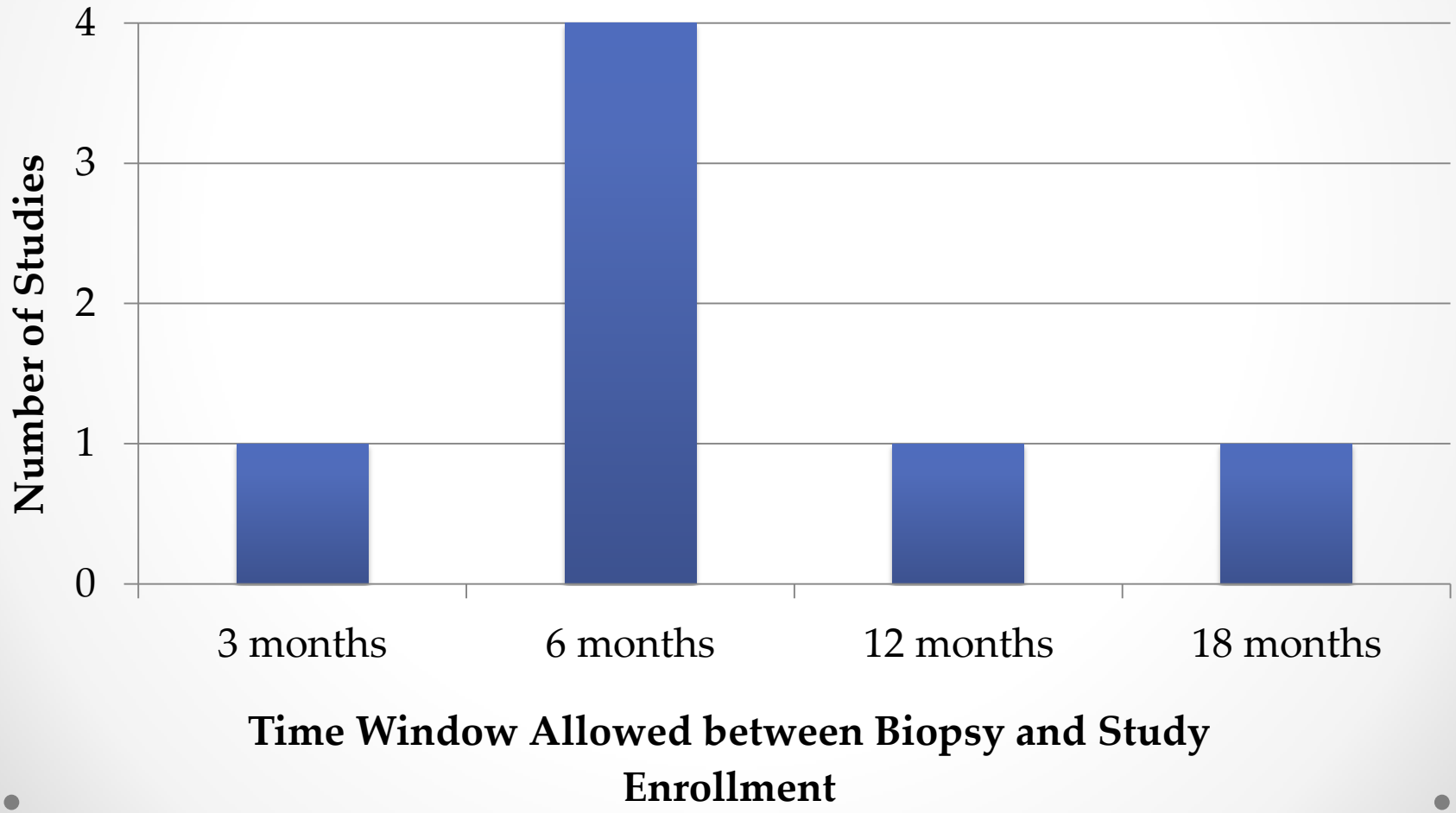
Table 1. Placebo-cohort baseline characteristics (n=404) cont.

Baseline Characteristics	Weighted Average*
Histology: Fibrosis stage	1.5
Histology: Total NAFLD activity score	5.0
Histology: Hepatocellular ballooning score	1.2
Histology: Steatosis score weighted	2.1
Histology: Lobular inflammation score	1.7

**Averages from each individual study were weighted based on placebo-arm sample sizes

Histologic evidence:

The 7 studies varied in the number of months allowed between liver biopsy and enrollment in the study as shown below:



Citations

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