Comparison of a Frailty Index Tool based on Clinical Assessment with one based on Routinely-Collected Laboratory Safety Data: Links Between Frailty, Adverse Events, and Function in the Setting of an Alzheimer's Disease Clinical Trial

Justin Stanley BScE[1], Taylor Dunn MSc[1], Lisa M McGarrigle PhD[1,2], Susan E Howlett PhD[1,2], Arnold B Mitnitski PhD[1,2], Kenneth Rockwood MD[1,2]
[1]DGI Clinical Inc., Halifax, NS Canada; [2]Dalhousie University, Halifax, NS Canada

Background

Grades of frailty can be quantified with a frailty index (FI) using either clinically apparent health deficits (FI-Clinical) or deficits detected by laboratory tests (FI-Lab)[1]. in this exploratory analysis of the double-blind Video Imaging Synthesis of Treating Alzheimer disease (VISTA) galantamine trial we constructed both an FI-Clinical, and, employing safety data, an FI-Lab.

Our objectives were to:

1. compare FI-Lab and FI-Clinical scores and
2. use these scores (and their composite - FI-Combined) to investigate associations with:
   - Frailty,
   - Adverse events (AEs)
   - Function

Methods

Design and Subjects

- VISTA was a four-month, double-blind, placebo-controlled trial followed by a four-month, open-label, follow-up phase in which all participants received galantamine.
- At baseline, participants had mild-moderate dementia, as assessed by Mini-Mental State Examination (MMSE) and Disability Assessment for Dementia (DAD) scores.

Frailty Index variants

- Each Frailty Index was scored by summing the number of deficits (0 indicating normal and 1 = abnormal) divided by the total number of deficits measured to yield a score between 0 and 1
- FI-Clinical was constructed using 34 co-morbidities, physical deficits, and neurological function data from clinical assessments.
- FI-Lab was constructed from 45 standard laboratory test results.
- FI-Combined was created from all 79 items.

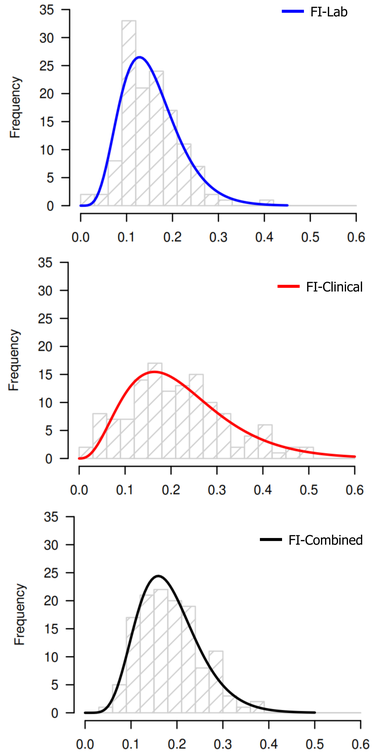
Table 1. Baseline Subject Characteristics by Baseline Frailty Level[a]

	Total N = 130	Low FI N = 81	High FI N = 49	P-value[b]
N (% of Subjects):				
Treated	64 (49)	36 (44)	28 (57)	0.222
Women	82 (63)	50 (62)	32 (65)	0.824
Mean (SD):				
Age	77.2 (7.8)	75.4 (7.5)	80.2 (7.2)	<0.001
MMSE	20.3 (3.8)	20.8 (3.5)	19.5 (4.1)	0.060
ADAS-cog	26.2 (7.6)	25.4 (7.4)	27.4 (7.8)	0.151
DAD	73.4 (20.7)	76.5 (19.4)	68.3 (22.0)	0.032
AEs	4.2 (4.1)	3.3 (3.2)	5.8 (5.0)	0.002
Con-Com't Meds	9.3 (6.8)	7.0 (5.1)	13.2 (7.6)	<0.001
FI-LAB	0.15 (0.06)	0.13 (0.04)	0.20 (0.06)	N/A
FI-Clinical	0.22 (0.11)	0.16 (0.07)	0.32 (0.08)	N/A

Abbreviations: ADAS-cog, Alzheimer Disease Assessment Scale-cognitive subscale; AEs, Adverse Events; Con-Com't Meds, Concomitant Medications; DAD, Disability Assessment for Dementia; FI, Frailty Index; MMSE, Mini-Mental State Examination; SD, Standard Deviation. [a]Low FI, FI-Combined ≤ 0.2; High FI, FI-Combined > 0.2. [b]p-values < 0.05 were considered statistically significant.

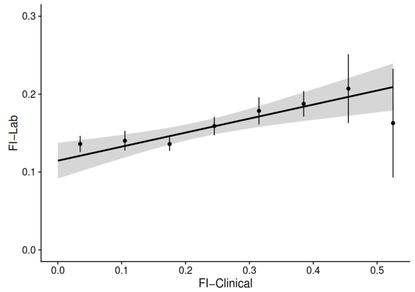
Results

Figure 1. Baseline FI scores exhibited distinct frequency distributions



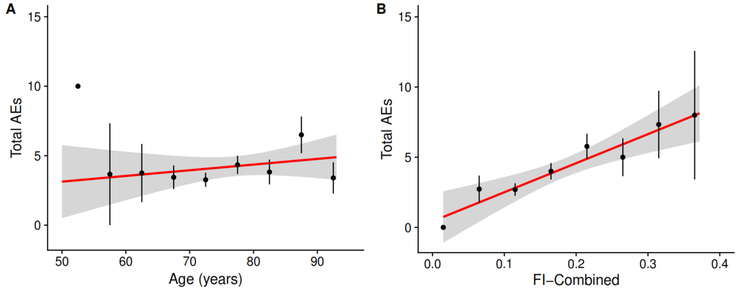
Frequency distributions of FI scores are shown in intervals of 0.03. Data were fit to a gamma distribution and tested using the Kolmogorov-Smirnov test.

Figure 2. The laboratory deficits FI was correlated with the clinical deficits FI.



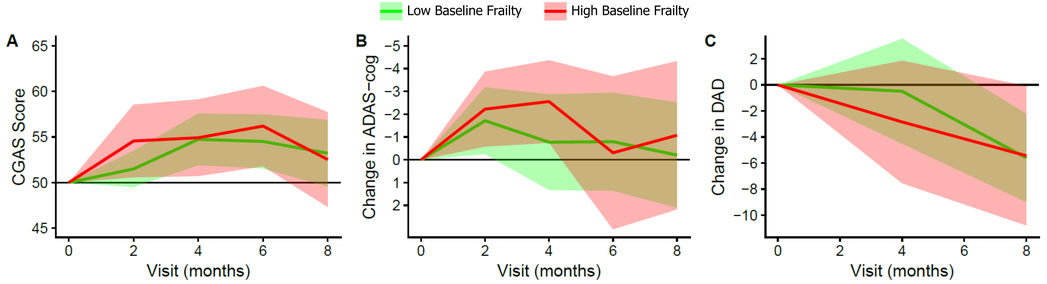
Clinical FI scores were pooled in intervals of 0.07. The mean ± SEM FI-Lab scores were taken for each interval and plotted against FI-Clinical scores and fit with a linear regression (**r=0.32**; p<0.001), shown with the 95% CI band.
Abbreviations: CI, Confidence Interval; FI, Frailty Index; SEM, Standard Error of the Mean

Figure 3. Compared with age, the baseline composite Frailty Index better predicted the total number of adverse events experienced throughout the trial.



The mean ± SEM AEs are shown, plotted against age (A) in 5 year intervals or FI-Combined (B) by 0.05 FI intervals. Data were fit with a linear regression (A: r=0.077, p=0.385; B: r=0.338, p<0.001) with the 95% CI band shown.
Abbreviations: AEs, Adverse Events; CI, Confidence Interval; FI, Frailty Index; SEM, Standard Error of the Mean

Figure 4. Individuals with high and low baseline frailty scores showed similar treatment effects



The mean scores (with 95% CI band) for subjects being treated with galantamine are shown by frailty level. At the end of the double-blind phase (4 months), subjects, being treated, with low baseline frailty (FI-Combined < 0.20) performed similarly to those with high baseline frailty (CGAS 54.7 vs 54.9, p=0.945; ADAS-cog -1.0 vs -2.6, p=0.212; DAD -0.5 vs -2.8, p=0.459). However, compared to placebo, subjects with low frailty saw a larger difference between treatment arms in clinician-rated GAS (SRM = 0.51 versus 0.22) and change in DAD scores (0.35 vs 0.18) but not with change in ADAS-cog scores (-0.13 vs -0.51).
Abbreviations: ADAS-cog, Alzheimer Disease Assessment Scale-cognitive subscale; CGAS, Clinician-rated Goal Attainment Scaling; CI, Confidence Interval; DAD, Disability Assessment for Dementia; SRM, Standardized Response Mean.

Summary of Results

- The distributions of FI scores were skewed towards 0 and differed significantly from a normal distribution (Shapiro-Wilk test: FI-Lab, p=0.004; FI-Clinical, p=0.013; FI-Combined, p=0.006)
- The mean (±SD) FI-Combined score was 0.18±0.07 (n=130; range=0.05-0.37).
- Frailty increased with age (FI-Lab: r=0.23, p=0.01; FI-Clinical: r=0.35, p<0.001; FI-Combined: r=0.36, p<0.001)
- FI-Combined scores were closely associated with more AEs (r=0.34, p<0.001) and worse DAD scores (r=-0.19, p=0.03); individual FIs were less well correlated.
- FI-Lab and FI-Combined scores were both correlated with worse baseline MMSE scores (FI-Lab: r=-0.19, p=0.03; FI-Combined: r=-0.21, p=0.02).

Discussion and Next Steps

- Frailty index scores derived from laboratory deficits using safety data in the VISTA trial were correlated with frailty index scores derived from clinical assessments.
- The use of all available deficits to construct a frailty index (FI-Combined) yielded better, more highly correlated, associations between measures.
- FI-Combined scores were associated with outcome measures and subject characteristics. Increasing baseline frailty was related to:
  - older age,
  - greater use of concomitant medications,
  - worse baseline cognition (Mini-Mental State Examination),
  - worse baseline function (Disability Assessment for Dementia),
  - more adverse events.
- Although the number of adverse events increased with frailty, subjects with higher baseline Frailty Index scores saw the same, positive, treatment effect as did subjects with lower baseline Frailty Index scores.

CONTACT posters@dgiclinical.com

ABBREVIATIONS

ADAS-cog: Alzheimer's Disease Assessment Scale Cognitive subscale
AEs: Adverse Events
CGAS: Clinician-rated Goal Attainment Scaling
CI: Confidence Interval
Con-Com't Meds: Concomitant Medications
DAD: Disability Assessment for Dementia
FI: Frailty Index
MMSE: Mini-Mental State Examination
SD: Standard Deviation
SEM: Standard Error of the Mean
SRM: Standardized Response Mean

REFERENCES

[1]Howlett, S. E., Rockwood, M. R., Mitnitski, A., & Rockwood, K. (2014). Standard laboratory tests to identify older adults at increased risk of death. *BMC Medicine*, *12*, 171. http://doi.org/10.1186/s12916-014-0171-9