Establishing clinical meaningfulness in rare/orphan disorder clinical trials – the role of the CGI

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Disclosures

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Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

CGI - Background

- Originated with Guy et al 1976
- Utilized in multiple pivotal clinical trials as a co-primary or key secondary outcome measure over the past 45 years
- Three versions:
  - CGI-I/C – most applicable in chronic (e.g. neurodevelopmental) disorders
  - CGI-S – most applicable in severe episodic disorders (e.g. bipolar disorder, Tourette syndrome)
  - CGI Efficacy Index – used for third party reimbursement
- CGI-I conventions:
  - 1-point change is considered “clinically meaningful”
  - Score of 1, 2, or 3 = “clinical benefit”
  - Score of 1 or 2 = “response”

UNC Developmental Neuropharmacology Clinic

- CGI-S/I and Efficacy Index completed on every outpatient, at every clinic visit, from 1988 through 2002 (n ≥ 500).
- Syndrome-specific rating scales simultaneously completed by clinicians and caregivers (e.g. CARS, Edelbrock CAP Scale, Iowa Conners, CPTQ, CDI, HAM-D, YMRS, YGTSS, YBOCS, CMAS, etc)
- 10%, 15%, and 20% thresholds identified for CGI-I movement of 1-point
  - Early understanding of MCIDs and MIDs in rare and non-rare neurodevelopmental disorders
- Presented at ANPA Annual Scientific Meeting in February 1998
- Data was leveraged by two different companies that led to two separate sNDA approvals

The Role of the CGI-S/I in the Trofinetide Clinical Development Program for RTT

- CGI-S/I was first introduced in Phase 2a study (commenced in 2013) – first time it was used in this therapeutic area (Rett syndrome = RTT)
- An anchored rating grid was developed (see Neul et al., 2015)
- The therapeutic area benefitted from a longtime natural history study, a tight study culture, “observable” outcome measures, and a ready ability to identify a gold standard clinician rater
- The CGI-I was a core component of group-level and subject-level results analyses in Phase 2 (see Glaze et al., 2017)
- The CGI-I ultimately served as a co-primary in the pivotal Phase 3 program that led to this drug’s approval in 2023 for the treatment of Rett syndrome

MCIDs and MIDs in the Trofinetide RTT Phase 2a Study

- 10%, 15%, and 20% change-from-baseline thresholds agreed as clinically relevant on the ordinal scales, in the composite approaches
  - For the CGI-I, the thresholds were 0.5 at the group level and 1 at the individual level
  - Vetted through round-table discussion with PIs and patient advocacy groups
- Group level analyses included a concordant trend analysis and permutation testing, and analyses also included individual scorecard approach
- The individual scorecard approach (-1, 0, +1 for each measure in the scorecard) occurred independent of, but concurrent with, the genesis of the MDRI
- The results predicted/foreshadowed a successful clinical development outcome for trofinetide
- See Glaze et al., 2017

Evolution of the CGI-S/I in Rare/Orphan Disorders, e.g. Angelman syndrome

- The CGI-I (albeit a syndrome-specific version) was the primary outcome measure in the gaboxadol Phase 3 program in Angelman syndrome (see Kolevzon et al., 2021)
- Three separate versions of the CGI were spawned in Angelman syndrome clinical development programs from three different sponsors
  - Utilized different anchoring schemes and different Likert scales
  - The global CGI scores were very well correlated
- The CGI-I has been more sensitive at detecting change/benefit than the Bayley and the Vineland (30% of gains that occurred in ASO trials were missed by the latter measures)
- Domain CGIs have become common in these clinical trials
  - Domain CGIs use the same Likert scale as the CGI-I
  - Sleep, Behavior, Communication, Fine Motor, Gross Motor, ADLs
  - A global (overall) CGI is always included, along with the domain CGIs

The CGI in Angelman Syndrome – Example 1

DOMAIN	SEVERITY = 1	SEVERITY = 2	SEVERITY = 3	SEVERITY = 4	SEVERITY = 5	SEVERITY = 6	SEVERITY = 7
	Normal, Not at all Impaired	Borderline, Slightly Impaired	Mildly Impaired	Moderately Impaired	Markedly Impaired	Severely Impaired	Among the Most Extremely Impaired
Behavior	Normal; typical child	**May interfere** with day-to-day functioning	**Mildly interferes** with day-to-day functioning. **May start** to impact outings to community	**Moderately interferes** with day-to-day functioning. Community outings **may** require preparation	**Markedly interferes** with day-to-day functioning. Community outings are only possible with **modest** preparation	**Severely interferes** with day-to-day functioning. Community outings are only possible with **extensive** preparation	**Profoundly interferes** with day-to-day functioning. Outings to community are **rare**
Motor (Fine)	Normal, age-appropriate	Uses utensils to eat	Uses utensils independently to eat, but makes a mess while eating	Requires hand over hand assistance to use utensils to eat	Uses hands to eat	Uses hands to eat but severely limited	Unable to use hands to eat
Motor (Gross)	Normal. age-appropriate	Runs well, slight difficulty with consecutive tandem gait steps, independently walks up/downstairs	Runs clumsily, walks independently, uses stairs with support	Walks but may require one hand support	Cruises, walks with two hands held and/or with support, including walker or crutches	Pulls/pushes self to stand, and/or crawls on hands and knees	Completely wheelchair-dependent
Expressive Communication	Normal. age-appropriate	Able to use combined words to form phrases	Able to use ≥ 5 single words with intent	Able to use at least one word with intent	Able to make consonant sounds sometimes with intent	Able to make vowel sounds sometimes with intent	Able to make sounds without intent
Receptive Communication	Normal. age-appropriate	Understands simple concepts and conversations	Understands a 2-step command	Understands a 1-step command	Understands "no", own name and ~5 words	Orients to voice but no apparent understanding of language	No response to language or voices
Sleep	Typical. Falls asleep within 30 minutes; sleeps throughout the night	Takes 31-60 mins to fall asleep (1-2 nights per weeks. Child awakens caregiver during the night, **1-2 times per week**	Takes 31-60 mins to fall asleep (≥ 3 nights per weeks. Child awakens caregiver during the night, **3-5 times per week**	Takes between 1-2 hours to fall asleep (1-2 nights per week). Child awakens caregiver almost **every night**	Takes between 1-2 hours to fall asleep (≥ 3 nights per week). Child awakens caregiver **several times during the night**	Takes more than 2 hours to fall asleep (1-2 nights per week). Child does not sleep more than 4 hours continuously	Takes more than 2 hours to fall asleep (≥ 3 nights per week), highly dysregulated and unpredictable sleep

Kolevzon et el., 2021, J Neurodev Disord

The CGI in Angelman Syndrome – Example 2

SAS-CGI

SAS-CGI – Severity

None	Very mild	Mild	Moderate	Severe	Very severe	Notes to explain rating
☐	☐	☐	☐	☐	☐	

SAS-CGI – Change

Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse	Notes to explain rating
☐	☐	☐	☐	☐	☐	☐	

CASS

CASS – Impact

Not at all difficult	A little difficult	Somewhat difficult	Quite difficult	Very difficult
☐	☐	☐	☐	☐

CASS – Change

Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse
☐	☐	☐	☐	☐	☐	☐

CASS Caregiver-reported Angelman syndrome Scale; *SAS-CGI* Symptoms of Angelman syndrome - Clinician Global Impression

Connor-Ahmad et al, 2023, Orphanet Journal of Rare Diseases

A Cautionary Tale – Congenital Myotonic Dystrophy (CDM1)

- No prior history of clinical trials in CDM1 before tideglusib Phase 2 program
- No preceding multisite natural history study, no tradition of using clinical rating scales for measurement-based care, no treatment options – this all had an impact on the clinical acumen of clinician-raters
- Rigorous implementation of the CGI-S/I was very challenging
  - On reflection, a direct grid would have improved things greatly
- On a positive note, regulators (e.g. the MHRA) accepted a bespoke approach to establishing MCIDs and MIDs assisted by the CGI-I
  - A tabular approach was used that compared a 1-point change on the CGI-I to the adjacent degree of change on the ordinal rating scales and the functional/performance-based measures
  - The 10%/15%/20% thresholds for change-from-baseline were acceptable
  - This approach informed subsequent results discussions and sample size estimates

Patient/Caregiver CGI-I/C in Rare Neurodevelopmental and Neuromuscular Disorders

- CGI-S is not feasible, by definition
- Very difficult to establish a solid/consistent rating scale culture with the P-CGI-C
  - Each caregiver has an n = 1 reference point (i.e. their own child)
  - Difficult to dampen the impact of expectancy and gratitude
  - The influence of social media is difficult to gauge
- MIDs are directly influenced by their child's baseline level of severity
  - Higher degree of severity correlates with a smaller MID (Angelman syndrome)
- Open text fields are important secondary sources of information

Questions