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Commentary. Towards A Core Outcomes Assessment Set for Clinical High Risk

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1. Introduction

The clinical high risk (CHR) paradigm for psychosis was first articulated 25 years ago (Yung et al., 1995), and thus far no medication treatment has received regulatory approval specifically for CHR. One challenge for the development of new treatments is the well-known heterogeneity of CHR patients, both at ascertainment (Fusar-Poli et al., 2016) and over time (Addington et al., 2019). The concept of a core outcomes assessment set (COS) for CHR may aid in the dissection of heterogeneity and in progress toward new treatments.

2. What is a core outcomes assessment set?

A COS has been defined as “an agreed, standardized set” of outcome assessments “that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care” (COMET Initiative, 2020). COSs are generally sponsored by professional or governmental organizations: other examples include the International Consortium for Health Outcomes Measurement (ICHOM, 2020) and the PhenX Toolkit (PhenX, 2020). In addition the US Food and Drug Administration (FDA) released a Clinical Outcome Assessment Compendium (Center for Drug Evaluation and Research, 2019) to promote the incorporation of standardized outcomes in clinical trials and foster patient-focused drug development.

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Contributors

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Conflict of interest

Dr. Woods reports that he has received sponsor-initiated research funding support from Teva, Boehringer-Ingelheim, Amarex, and SyneuRx. He has consulted to Boehringer-Ingelheim, New England Research Institute, and Takeda. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists. Other authors report no disclosures.

3. Core outcomes assessment and CHR

Although it has long been known that other outcomes are important (Woods et al., 2001), most research in CHR to date has focused on conversion to psychosis. That said, some research has evaluated a number of potentially independent outcomes for CHR in addition to conversion, including continuous measures of symptoms (positive, negative, affective, or anxiety), cognition, or functioning and categorical measures such as response, remission, or recovery. These other outcomes could potentially represent more tractable treatment targets than conversion.

Several of these alternative CHR outcomes are addressed in in this Special Section. The positive symptom paper (Calkins et al., 2020) focuses on the Scale Of Psychosis-risk Symptoms (SOPS), which has been extensively used and described psychometrically (Woods et al., 2019). Exploratory factor analysis suggested the possibility of two factors that were unstable over time, although other analyses indicated a single-factor solution. Capturing the breadth of CHR psychopathology in rating scales is surely admirable, but individual items within multi-item subscales can follow different trajectories over time. This heterogeneity introduces noise into the analysis that can potentially sap statistical power. Analyses similar to those of Calkins et al using additional methods, such as Rasch modeling (Baandrup et al., 2020) and group-based multi-trajectory modeling (Allswede et al., 2020), should be employed in multiple large datasets to dissect this heterogeneity and maximize the potential for sensitivity to change in future clinical trials. The Special Section negative symptom review (Strauss et al., 2020) identifies a new instrument, the Negative Symptom Inventory-Psychosis Risk, that covers all five domains agreed upon in a 2006 NIMH consensus conference (Kirkpatrick et al., 2006) and is being developed using modern psychometric methods. The rating scale in the depression paper (Addington et al., 2020) was the Calgary Depression Scale for Schizophrenia, selected for its relative independence from positive and negative symptoms (Addington et al., 1996). The functioning paper (Carrion et al., 2020) featured the Global Functioning: Social and Global Functioning: Role scales (Cornblatt et al., 2007), simple single-item instruments with excellent psychometric properties (Carrion et al., 2019).

In addition to the alternative CHR outcomes, an editorial in the Special Section (Torous and Keshavan, 2020) addresses an alternative method of measuring outcomes. The development and validation of digital outcome measures employing smartphone technology promises considerable opportunity to contribute to treatment assessment, and validated digital outcome measures could become important components in CHR COSs.

4. Challenges and Opportunities

In reflecting on the papers in the Special Section, we see challenges and opportunities relating to the future development of CHR COSs: patient-rated outcomes (PROs), anxiety measurement, cognition, and high-throughput online data collection (HTODC).

Although not addressed by any Special Section paper other than the editorial, PROs provide valuable evidence about patient feelings, functioning, and treatment expectation that may

help support drug registration labeling claims (Food and Drug Administration, 2006, 2009). The relevant outcomes for patients can differ from those important to clinicians, caregivers, and payers (Fischer et al., 2002; Kuhnigk et al., 2012). While concerns have been raised about the validity of PROs in schizophrenia (de Pinho et al., 2018; Durand et al., 2015; Takeuchi et al., 2016), of 18 fully-reported CHR studies included in a recent treatment umbrella review (Fusar-Poli et al., 2019), 11 employed one or more PROs. Additional investigation is needed on validity and other measurement properties of PROs in CHR.

Several anxiety disorders are commonly comorbid in CHR, and anxiety comorbidity has been associated with poor functioning (Fusar-Poli et al., 2014) although not with conversion to psychosis (Fusar-Poli et al., 2014; Webb et al., 2015). Anxiety scales appropriate for a mixed group of anxiety types, however, have been relatively little used in CHR clinical trials. One trial (Bechdolf et al., 2011) employed the self-report State-Trait Anxiety Inventory (Spielberger, 1983), which as advantages of long use and quick administration along with good psychometric properties (Rose and Devine, 2014). The self-report Beck Anxiety Inventory (BAI) (Beck et al., 1988) has similar advantages but has not been used in CHR trials to our knowledge. The clinician-reported Hamilton Rating Scale for Anxiety (HRSA) (Hamilton, 1959) was used in one CHR trial (McGorry et al., 2002). The BAI and HRSA tend to focus on physical symptoms of anxiety and less on cognitive symptoms such as worry (Julian, 2011; Koerner et al., 2010) and so potentially could be less sensitive to change.

Cognitive impairment is a key feature of CHR (Seidman et al., 2016). Particularly if samples are enriched for cognitive impairment, this domain offers an important outcome for CHR, analogous to the Cognitive Impairment Associated with Schizophrenia outcome (Buchanan et al., 2005). Unfortunately, an attempted merger of cognition data across four large CHR consortia could find complete overlap on only one measure (HARMONY Investigators, 2019). A recent US funding initiative (US NIMH, 2019), however, may incentivize developing a core cognition battery for CHR.

HTODC offers another method to collect digital data in CHR and may offer expansion of samples beyond those close to an academic medical center (Gillan and Daw, 2016). In HTODC, subjects participate online, either anonymously or with electronic consent. Collection may include phenomenological data for deep phenotyping as well as behavioral and computationally-informed task performance (Kafadar et al., in press). HTODC can potentially be used exclusively in clinical trials of on-line interventions or as supplementary measures in studies of traditional in-person psycho- or pharmaco-therapies.

5. Conclusions

Taken together, these Special Section papers suggest that construction of a core outcomes assessment set for CHR is currently or may soon be feasible. Substantial additional work will need to be done to achieve a final composition of the set. In particular, many of the better-established instruments may not have solicited adequate patient input during their item development (Food and Drug Administration, 2006, 2009) and so may not meet current FDA standards for content validity. Areas such as patient-reported outcomes, anxiety,

cognition, and high-throughput online data collection offer additional challenges and opportunities.

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