Contemporary Clinical Trials 83 (2019) 27–36

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Pharmacogenetic clinical decision support for psychiatric hospitalization: Design of the CYP-GUIDES randomized controlled trial

Gualberto Ruaño[a,*], Theodore Holford[b], Richard L. Seip[c], John W. Goethe[d], Raveen Mehendru[e]

[a] Institute of Living at Hartford Hospital, Genomas Laboratory of Personalized Health, 67 Jefferson Street, Hartford, CT 06106, United States
[b] Yale School of Public Health, Yale University, 1 Church Street, 6th Floor Suite, New Haven, CT 06510, United States
[c] Metabolic and Bariatric Surgery Center, Hartford Hospital, 330 Western Boulevard, Glastonbury, CT 06033, United States
[d] Private Medical Practice, 155 Ayrshire Lane, Avon, CT 06001, United States
[e] Institute of Living at Hartford Hospital, 200 Retreat Ave, Hartford, CT 06114, United States

1. Introduction

The CYP-GUIDES *(Cytochrome Psychotropic Genotyping Under Investigation for Decision Support)* trial aims to establish evidence for clinical pharmacogenetics in psychotropic prescription in severely depressed inpatients. The use of drugs dependent on metabolism by the hepatic Cytochrome P450 2D6 enzyme (CYP2D6) is widespread in psychiatry. Demonstrating clinical utility of a method to identify and treat differently those patients who cannot metabolize these drugs is of interest to general healthcare. This trial may ultimately help develop *CYP2D6* genotyping and functional phenotyping for application of pharmacotherapy in the management of major depressive disorder (MDD), adding a crucial weapon in the battle against mental illness. This article describes the design of a Randomized Controlled Trial (RCT) of *CYP2D6* genotype-guided versus standard care psychotropic prescription which proposes to address this evidence gap.

Over 1.4 million hospitalizations for mental health conditions occur annually in the United States (3.4% of all hospitalizations), and more than half are for MDD. Hospitalization for MDD results in a course of treatment in the United States that averages 6.8 days at a cost of $2000 per day according to recent surveys [1]. The mean total cost per patient of such hospitalization is $13,600.

Average hospitalization length of stay (LOS) in U.S. psychiatric hospitals has been declining [2]. An increasing proportion of psychiatric patients are treated in outpatient settings [7], resulting in an inpatient patient mix that is severely ill. Some psychiatrists have expressed concern that psychiatric morbidity at discharge may be greater among patients with brief LOS, while others have voiced concern that patients with long LOS have relatively poor outcomes [3]. The conservation of resources serves as motivation to keep length of stay for psychiatric treatment short, but short LOS is associated with elevated risk of readmission [4].

Factors influencing psychiatric LOS include *(1)* patient demographics, psychosocial factors [5,6] and health insurance [7]; *(2)* clinical factors, including severity of illness [8], psychiatric diagnoses, and adherence to psychotropics; and *(3)* treatment, including quality of care [9], size of hospital staffs [10], psychiatrist caseloads [11], payer pressure for early discharge [12], and availability of community services [13]. Payer policies are a response to rising costs of psychiatric services [14]. LOS for MDD treatment and the rate of 30-day readmission comprise a *checks and balances* system [15]. Medicare has released rulings urging hospitals to track discharge [16], ensuring physicians follow patients and fill their prescriptions.

Despite these myriad factors, CYP-GUIDES is motivated by preliminary data from pilot clinical studies which support an important role for *CYP2D6* function with regard to drug utilization, LOS and readmission [17]. The involvement of CYP2D6 in metabolism of psychiatric drugs is significant [18]. Among antidepressants and antipsychotics, half are major substrates for CYP2D6. *CYP2D6* is a hyperpolymorphic and hypermutable gene, characterized by duplications, rearrangements, deletions, and diverse haplotypes [19]. Drug side effects are more frequent in patients with *CYP2D6* polymorphisms [20]. Psychiatric patients who carry *CYP2D6* gene alterations require longer hospitalizations compared to those without [21].

The CYP-GUIDES trial will assess whether clinical prescribing guided by CYP2D6 functional status can improve the treatment of psychiatric inpatients, shorten the length of hospitalization, and reduce readmission.

2. Design

2.1. Pilot studies and preliminary results

Our retrospective study [27] laying the groundwork for CYP-GUIDES aimed to determine the effect of the *CYP2D6* genotype and functional status on the inpatient LOS for patients treated for major depressive disorder at IOL (Fig. 1). A total of 149 inpatients were genotyped retrospectively to detect altered alleles in the *CYP2D6 gene*.

* Corresponding author.
E-mail addresses: gualberto.ruano@hhchealth.org (G. Ruaño), theodore.holford@yale.edu (T. Holford), richard.seip@hhchealth.org (R.L. Seip), raveen.mehendru@hhchealth.org (R. Mehendru).

https://doi.org/10.1016/j.cct.2019.06.008
Received 19 March 2019; Received in revised form 4 June 2019
Available online 24 June 2019

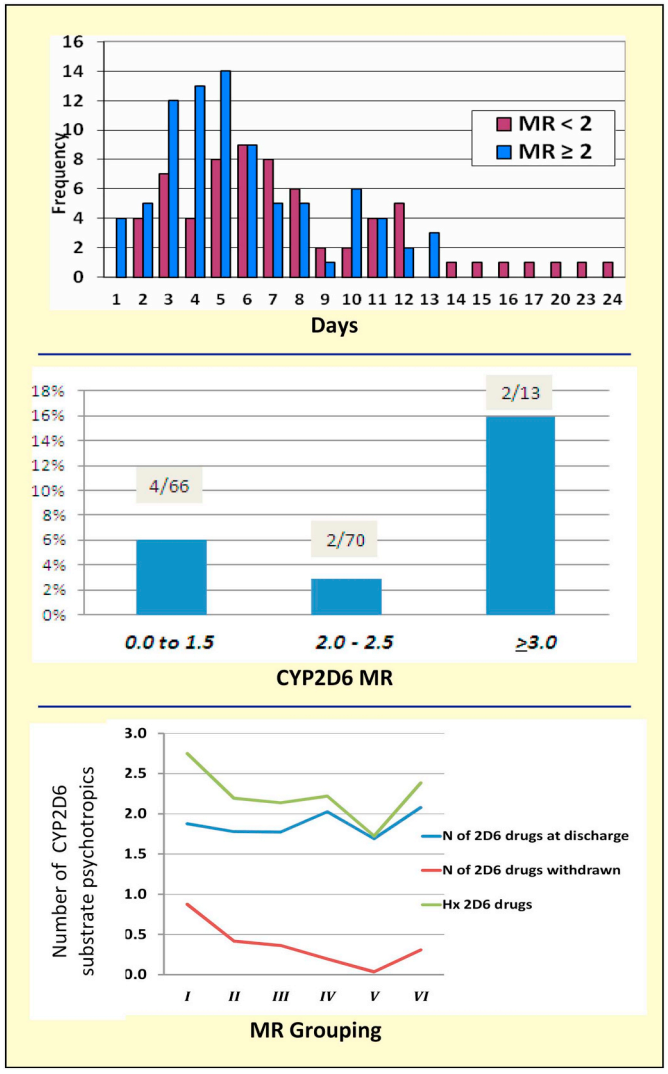

Fig. 1. Results of pilot studies. Hospitalization length of stay (LOS) *(Top panel)*. Readmission rate 30 days post hospital discharge *(Middle)*. Drug utilization comparison at hospital admission and discharge *(Bottom)*.

The Metabolic Reserve was determined by quantitative genotyping. During hospitalization, *CYP2D6* genotypes were unknown, and prescription changes were implemented on clinical considerations alone.

We examined *CYP2D6* genotype status in relation to inpatient LOS in a series of 149 consecutive, consenting admissions admitted to the HH IOL through the inpatient psychiatric services in January–March 2007. Patients ranged in age from 18 to 78 (median age 40) and were predominantly female (61%). All had a diagnosis of MDD and were treated with psychotropic medications. The study was approved by the Hartford Hospital IRB and each patient signed a statement of informed consent that included permission to use a blood sample for *CYP2D6* genotyping.

The CYP2D6 Metabolic Reserve (MR) index represents a series of quantitative phenotypes calculated by adding the functional score of the two CYP2D6 alleles carried by each patient [22,23]. In the cohort of 149 inpatients, we observed CYP2D6 MR index ranging from 0.0 to 3.0, indicative of patients ranging in functionality from none to high. The MR index score of 2.0 occurred most frequently ($N = 41$). MR values lower than 2.0 were represented as follows: 0.0 ($N = 3$), 0.5 ($N = 5$), 1.0 ($N = 36$), 1.5 ($N = 22$). MR values higher than 2.0 were represented as follows: 2.5 ($N = 29$), 3.0 ($N = 13$).

2.1.1. Length of stay (LOS)

We dichotomized the patient cohort according to CYP2D6 MR. "low" metabolic reserve included patients with MR scores of 0.0, 0.5, 1.0, or 1.5. "High" metabolic reserve included patients with MR scores of 2.0, 2.5, or 3.0. LOS was significantly *($p = .002$)* longer in low MR patients, 7.79 days (± 0.59 SE, $N = 66$), compared with high MR patients, 5.75 days (± 0.34 SE, $N = 83$) *(*Fig. 1*, top panel)*. The study demonstrated that the functional status of the *CYP2D6* gene can significantly impact utilization of psychiatric hospitalization services, and specifically is associated with longer LOS [17]

We applied multiple regression analysis using stepwise and backward elimination strategies to generate models to predict LOS in the cohort. *CYP2D6* MR index, classified as low (MR < 2) or high (MR ≥ 2), and all demographic and clinical variables were included in order to identify significant contributors to the LOS model. *CYP2D6* MR was the strongest predictor. It was twice as predictive as each of the other significant contributors, which were age, number of all psychotropics and number of CYP2D6-substrate psychotropics prescribed during hospitalization at IOL [17].

2.1.2. Readmission

After the hospitalization, patients were followed for hospital readmission 30 days post discharge [24]. We grouped patients into metabolizer status categories of "Low" Metabolic Reserve (MR < 2, $N = 66$ patients, 44%), and segregated the "High" into an intermediate subcategory (MR 2.0 or 2.5, $N = 70$, 47%) vs. ultrarapid subcategory (MR = 3.0, $N = 13$, 9%). We tested for differences in psychiatric hospital readmission 30 days after discharge across these 3 groupings using the chi square test. The number of patients re-admitted 30 days after discharge was 8, for a readmission rate of 5.4% (8/149). If proportional to the cohort, the low, intermediate, and ultrarapid categories would have had 3.5, 3.8, and 0.7 patients. Instead, the categories had 4, 2, and 2 patients, respectively *(*Fig. 1*, middle panel)*.

The readmission rate was 5.9% (4/66) for patients in the low MR grouping, 2.9% (2/70) for patients in the intermediate grouping, and 15.4% (2/13) for patients in the ultrarapid grouping (trend for difference between subgroups, *$p = .17$). Those readmitted within 30 days had a significantly higher rate of hospitalization within the past year (7/8, 88% vs. 69/140, 49%, $p = .04$). CYP2D6 functional status, among other factors, may affect 30-day readmission rate after psychiatric hospitalization in MDD patients.*

2.1.3. Drug utilization

Co-prescription of antidepressants and antipsychotics was prevalent during hospitalization, as 98% of all patients received antidepressants and 65% received antipsychotics. During hospitalization, of those patients on antidepressants, 45% received > 1; of those on antipsychotics, 12% received more than one. A total of 17 different CYP2D6-substrate psychotropic drugs (11 major, 6 minor) were taken by these patients (10 antidepressants, 7 antipsychotics). The average number of different CYP2D6-substrate drugs prescribed per patient was 2.1 ± 1.0. We compared the number of different CYP2D6-substrate medications prescribed at admission and during hospitalization to those prescribed at discharge for each patient to determine prescription changes during hospitalization.

Drug prescribing patterns were related to CYP2D6 Metabolic Reserve in the absence of patient genotype [25]. We assessed the effect of CYP2D6 MR on prescription changes using one-way ANOVA (linear model) and Sidak post hoc tests. MR significantly affected prescription changes *($p = .002$)* *(*Fig. 1*, bottom panel)*. Patients with very low MR (0.0 or 0.5, $N = 8$) *{Grouping I}* had the most prescription changes (0.88 drugs ± 0.30 SE). These differed significantly from patients with normal Metabolic Reserve [MR 2.0, $N = 41$ (0.20 drugs ± 0.06 SE, $p = .02$) *{Grouping IV}* and MR 2.5, $N = 29$ (0.03 drugs ± 0.03 SE, $p = .002$) *{Grouping V}*] who had the least changes in the cohort. Patients with ultrarapid MR (3.0, $N = 13$) *{Grouping VI}* had more

changes (0.31 drugs ± 0.13 SE) than patients with normal MR (2.0 or 2.5). Patients with intermediate Metabolic Reserve [MR 1.0, $N = 36$ (0.42 drugs ± 0.12 SE) *{Grouping II}* and MR 1.5, $N = 22$ (0.36 drugs ± 0.14 SE) *{Grouping III}*] were intermediate between those very low and normal.

We concluded that there was a significantly greater reduction in the number of CYP2D6-substrate drugs prescribed to MDD patients with null or poor CYP2D6 MR during hospitalization, compared to patients with normal MR. Patients with deficient and rapid MR were intermediate. Empirical psychotropic management during hospitalization is more intricate in patients with altered (subnormal or rapid) CYP2D6 MR. Determination of CYP2D6 functional status at admission could improve psychotropic prescription during hospitalization and optimize overall utilization of psychiatric services.

Building on these findings, CYP-GUIDES is a prospective RCT comparing outcomes in patients with major depressive disorder (MDD) treated according to the patient's *CYP2D6* functional status versus empiric standard care psychotropic selection [26]. The hypothesis was that provision of medication prescribing guidance based on the functional status of the patient's CYP2D6 enzyme inferred from genotype results will alter medication utilization resulting in a reduction of LOS during hospitalization and a lower readmission rate after discharge.

2.2. Recruitment and operations

The RCT will be conducted at a single site, the Institute of Living (IOL) at Hartford Hospital. The RCT was registered in ClinicalTrials.gov as *Pharmacogenetic Decision Support IT System for Psychiatric Hospitalization: RCT (CYP-GUIDES)* and assigned identifier NCT 02120729 in the registry [27].

The IOL established and operated the Clinical Evaluation and Monitoring System (CEMS), an innovative electronic messaging system. The clinical Laboratory of Personalized Health (LPH), which is onsite at Hartford Hospital, performed *CYP2D6* genotyping and functional phenotyping. *CYP2D6* genotype analysis detects all known common polymorphisms that result in an enzyme with null, reduced or rapid function. In the RCT, CEMS transmitted clinically actionable guidance based on the patient's genotype to the physician.

2.2.1. Recruiting pool and expectations for recruitment of patients with mental illness

The staff of the IOL is quite experienced in recruiting patients with mental illness to participate in research studies. For the pilot study of 149 patients with MDD, staff approached 224 qualified patients. The IOL admits ~350 patients with MDD per quarter, for an average of 27 patients per week. We therefore can project 27 approachable qualified patients per week. Based on past recruiting success, we will have to attempt to recruit 10 patients per week in order to enroll an average of 6.7 patients per week, which is sufficient to achieve enrollment at a rate of 325 patients per year.

2.2.2. Inclusion/exclusion criteria

The following will constitute criteria for Inclusion: *(a)* men or women aged 18 y or older, *(b)* patients who have been admitted to the Institute of Living and having a diagnosis of major depressive disorder, *(c)* ability to understand the requirements of the trial, *(d)* ability to comply with trial procedures and protocol. A woman is eligible to enter the trial if she is of child-bearing potential and not pregnant or nursing. The following constitute criteria for Exclusion: *(a)* children and adolescents, *(b)* hospital admission within previous 30 days of current admission, *(c)* history of dementia or Alzheimer's disease, *(d)* history of chronic kidney disease, *(e)* surgery within 6 weeks, *(f)* ischemic stroke within 6 weeks, *(g)* any history of hemorrhagic stroke or subarachnoid hemorrhage, *(h)* current enrollment in an investigational drug or device study that has not reached the time of the primary end point.

Recruitment may present challenges but we expect to be able to enroll sufficient numbers of qualified patients for the trial. The clinical coordinator must to approach 10 qualified patients per week in order to successfully recruit 6.5 patients per week for 50 weeks of each year to achieve 325 patients enrolled per year. The coordinator will be able to quickly identify patients admitted on Sunday nights through Thursday nights who also qualify according to the inclusion/exclusion criteria.

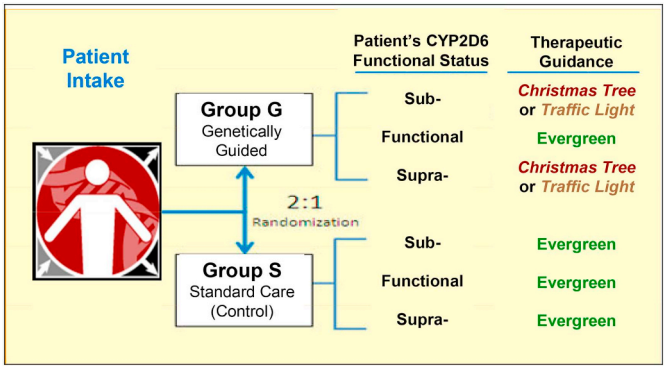

Fig. 2. Design of the CYP-GUIDES Randomized Controlled Trial.

The RCT will test the effects of therapeutic guidance, based on *CYP2D6* functional status, delivered via CEMS. The RCT planned to assign 1500 patients 2:1 to *Genetically-guided* therapy (*Group G*) for whom genotyping result and treatment recommendations are furnished via CEMS to the physician versus *Standard care* (*Group S*) for whom *CYP2D6* functional status is determined but not transmitted to the treating physician (i.e. empirical psychotropic therapy) (Fig. 2). For patients in *Group G* who are sub- or supra-functional metabolizers, medications primarily metabolized by the CYP2D6 enzyme are proscribed. Patients were advised about the trial and consented at the IOL by an assigned clinical coordinator trained by the psychiatric nursing staff.

2.2.3. Randomization

We designated assignment to *Group G* or *Group S* after genotyping. The random assignment is independent of genotype results. We will employ ISAAC, a 64 bit shift MD5 program typically used for encryption, but here adapted for random assignment. The program was utilized to derive a table of assignments for patients 1 through 1500 at the beginning of the trial. This table will be utilized throughout the trial. The method used for this study is therefore equivalent to *simple block randomization* with the block being the entire study. The outcome is predetermined and mathematically correct, different from a statistical random assignment generated at time of intake for each patient. Nevertheless, it certainly will be important to examine the randomization achieved in the trial at the resolution of individual alleles, allele combinations (diplotypes), and functional scoring (Metabolic Reserve). We intend to control for any imbalances in the analysis phase of the study as an alternative strategy.

There will be some buccal swab samples yielding DNA of low amounts or poor quality that fails to genotype (drop-outs). Patients whose DNA fails to genotype cannot be randomized to either *Group G* or *Group S*, but could be followed for length of stay and readmission and retained as part of total cohort data.

2.2.4. Protection of human subjects

We developed an appropriate and institutionally-approved informed consent (Hartford Hospital Institutional Review Board Protocol RUAN004090HE). The document informs participants of risks and benefits of participation in the research. It includes provisions for cheek cell swabs as sample source of DNA and storage of DNA for 1 year from the trial. The RCT also established a Data Safety Monitoring Board (DSMB) to review data every 6 months for the purpose of monitoring safety and efficacy and request statistical analyses in order to make

Table 1
CYP2D6 alleles, quantitative genotyping and functional scoring for the calculation of the Metabolic Reserve (MR) index.

Allele	Gene nucleotide Δ	Effect	Enzyme activity	Score
**1*	Reference	Normal	Functional	**1.0**
**1XN*	Gene copy number	> 1 gene copy/ locus	Increased	**2.0**
**2*	1661 G > C	Normal	Functional	**1.0**
**2a*	−1584C > G	Promoter	↑ transcription	**1.5**
**2XN*	Gene copy number	> 1 gene copy/ locus	Increased	**2.0**
**3*	2549 delA	Frameshift	None	**0**
**4*	1846 G > A	Splicing defect	None	**0**
**4XN*	Gene copy number	> 1 gene copy/ locus	None	**0**
**5*	Gene deletion	0 transcript copy	None	**0**
**6*	1707 delT	Frameshift	None	**0**
**7*	2935 A > C	H324P	None	**0**
**8*	1758 G > T	G169X	None	**0**
**9*	2615–2617 delAAG	K281del	Decreased	**0.5**
**10*	100C > T	P34S	Decreased	**0.5**
**11*	883 G > C	Splicing defect	None	**0**
**12*	124 G > A	G42R	None	**0**
**14*	1758 G > A	G169R	None	**0**
**15*	137_138 InsT	Frameshift	None	**0**
**17*	1023C > T	T107I	Decreased	**0.5**
**29*	1659 G > A, 3183 G > A	V136I, V338 M	Decreased	**0.5**
**35*	−1584C > G, 31 G > A	Promoter, V11 M	↑ transcription	**1.5**
**41*	2988 G > A	Splicing defect	Decreased	**0.5**

recommendations. The main duty of the DSMB is to evaluate the safety of the research and the data integrity of the results.

2.3. CYP2D6 genotyping and functional status

The coordinator will collect the buccal swabs for each inpatient, and delivered these to LPH. DNA was extracted from mucosal tissue and *CYP2D6* genotyped. We classified the alleles into clinically distinct categories as *null, deficient, normal,* or *rapid* based on well-defined molecular properties of the altered genes (Table 1). *Null* alleles lack any enzymatic activity because the altered gene does not produce a functional protein. Such null alleles include gene deletions *(*5)*, frameshift mutations *(*6)*, splicing defects *(*4)*, and null duplications *(*4XN)*. *Deficient* alleles have subnormal enzymatic activity due to nucleotide substitutions resulting in amino acid changes in the protein, and these variants may manifest subnormal enzymatic activity for some drug substrates *(*9, *10, *17, *29, *41)*. The *reference* allele refers to the normal allele *(*1)* and the enzymatically normal *(*2),* with enzymatic activity considered normal. *Rapid* alleles exhibit increased enzymatic activity as a consequence of either gene duplication *(*1XN, *2XN)* or a promoter polymorphism *(*2a, *35)*.

2.3.1. Metabolic Reserve (MR) index

We employed the *Metabolic Reserve (MR) index* to quantify the functional status of CYP2D6. The MR index provides numerical phenotyping analogous to "gene dosing" [28,29]. MR is calculated by adding the functional score of each of the 2 *CYP2D6* alleles for each patient (Table 1). Null alleles are assigned a value of 0.0; deficient alleles, 0.5; normal, 1.0; rapid, 1.5; and functional duplications, 2.0. The Metabolic Reserve index underlies a series of categorical *CYP2D6* metabolic phenotypes ranked as *sub-functional* (MR 0.0, 0.5 or 1.0), *functional* (MR 1.5, 2.0 or 2.5), and *supra-functional* (MR 3.0 or 3.5).

2.4. Therapeutic guidances

Blinding of physicians treating patients in *Group S* and *Group G* to *CYP2D6* genotype results was accomplished after carefully considering the implications, including experimental biases from having these results communicated or withheld. Neither patient nor physician knew the *Group* assignment. The physician was provided with therapeutic guidance for all patients in a color-coded tabular format: red, *avoid;* yellow, *prescribe with caution*; green, *prescribe as usual.* The drug guidance charts were assembled to represent commonly used antidepressants, antipsychotics, and stimulants.

There were 3 guidance charts where all the drugs were colorized according to their suitability for patients of different *CYP2D6* functionalities: *(a) Evergreen,* where all drugs are colorized green and can be prescribed as usual; (*b) Christmas Tree*, where major substrate drugs are colorized red, indicating proscription, and the others green; and *(c) Traffic Light,* where minor substrate drugs are also colorized yellow, indicating caution (Fig. 3). In the case of *Group S*, the guidance provided for all patients would be the *Evergreen* drug chart, regardless of the patient's *CYP2D6* functional status. In the case of *Group G*, drug chart choices among the 3 options would depend on the patient's *CYP2D6* function. For patients at the extremes of function (MR 0.0 or 3.5) the guidance provided is a *Traffic Light* chart while for those with abnormal function (MR 0.5, 1.0 or 3.0) the guidance is a *Christmas Tree* chart. In *Group G*, the *Evergreen* chart is provided only for the patients with normal function (MR 1.5, 2.0 or 2.5).

2.4.1. Clinical Evaluation and Monitoring System (CEMS)

The Behavioral Health Care Information System (BHCIS) was the electronic healthcare record at the IOL and CEMS is embedded within it. Developed with experts in artificial intelligence to help address factors cited for non-acceptance of existing expert systems, CEMS evolved over a period of 25 years as a unique tool to ensure consistent delivery of services to psychiatric inpatients at the Institute of Living [30,31]. CEMS interfaced directly with laboratory and pharmacy databases, and that supplanted advice dispensation with an innovative clinical monitoring system. CEMS was implemented in the RCT as a singular and innovative tool to advance healthcare administered to psychiatric inpatients. During the trial, CEMS would provide the Clinical Decision Support tool for monitoring delivery of appropriate care. It fulfills a vital role to ensure delivery of best clinical practices to IOL inpatients.

The primary physician acknowledges receipt of the alert and takes action by clicking on the *Action* button and selecting *Suspend. Suspend* is the only choice available to the physician. The primary physician can select a pre-approved rationale from an alert-specific checklist or respond with free-text. All free-text is reviewed by the Medical Director or designee.

In the RCT, we would employ CEMS to track responses of physicians to receipt of the drug guidances for the inpatient. The following alerts were installed in CEMS with the wording *Consider change in current prescription due to CYP2D6 functional status: (a)*Alert #9803: If *CYP2D6* result entered in CEMS is *"Christmas Tree"* and patient is receiving a Red drug, alert-specific guide links to a Portal which displays the list of Red and Green drugs; *(b)*Alert #9802: if *CYP2D6* result entered in CEMS is "*Traffic Light"* and patient is receiving a Red or Yellow drug, alert-specific guide links to a Portal which displays the list of Red, Yellow, and Green drugs. The physician responded to the alert by using a 4-item checklist: *(a)* Will switch to another medication not metabolized by CYP2D6; *(b)* Currently tolerating and responding well to this medication; *(c)* History of good response to and tolerance of this medication; and *(d)* Other *(free text mandatory)*.

The Portal was developed to be HIPAA compliant and provided automated email notifications and electronic systems to deliver the *CYP2D6* genotypes and therapeutic guidances to treating physicians in "read only" or "view only" format. The success of the trial will depend on the delivery of therapeutic guidances to treating physicians within 48 h of admission of the enrolled patient. We established and tested the online Portal, to provide the *CYP2D6* functional status result and corresponding drug-prescribing guidance.

Fig. 3. Therapeutic guidances provided in color-coded drug charts denoted by *Evergreen* (top panel), *Christmas Tree* (middle), and *Traffic Light* (bottom).

3. Statistical considerations

3.1. Length of stay (LOS)

We propose that genotyping information provided within 48 h of patient admission together with the guidances delivered by CEMS are nimble enough to affect the course of inpatient treatment. This claim depends in part on a timely delivery of the CYP2D6 guidance and prompt response to alerts received by the physician. Physicians do in fact respond quickly to alerts, validating our approach and making our claim testable. When physicians receive a CEMS alert on a laboratory test within 24 h of a morning blood draw, 89% will acknowledge receipt of the alert within 12 h, for a total of 36 h from a blood draw to response.

We are interested in the overall effect of *CYP2D6* guided psychotropic therapy in *Group G* vs. *Group S*. This is a simple comparison of the mean length of stay. Ordinarily this calls for a *t*-test. We observed a difference of 2.2 days in LOS based on CYP2D6 functionality and have also found that the variance around LOS is likely to differ from one group to the next. Accordingly we will use the Satterthwaite F-test [32] as an alternative to a simple t-test to test for the overall difference in LOS in *Group G* vs. *Group S* because it accommodates samples with difference variances about the mean. We establish sample size for the proposed trial to provide sufficient statistical power (1-β = 0.80, or 80%) to detect a difference of 0.6 days at a significance level of alpha = 0.05 (Table 2).

3.1.1. Determination of sample size estimate for LOS

Of 1000 patients who will be recruited into *Group G*, only a fraction of them, determined by CYP2D6 functional status, will be exposed to proscription of CYP2D6-substrate drugs. In this fraction, the proscription of CYP2D6 dependent drugs will reduce LOS by at least two mechanisms that reduce trial-and-error. Proscription will *(1)* stimulate withdrawal of CYP2D6-substrate drugs in patients who may be taking these at the time of admission, and *(2)* reduce the total number of drugs available to be tried.

We take into account the following facts: 31.5% of patients are expected to carry genotypes that denote sub-functional status (MR 0.0, 0.5 or 1.0). This group of patients represents the low end of the MR index spectrum and had a length of stay that was 2.2 days longer in our pilot study. A greater number of CYP2D6-substrate drugs were removed from low MR subgroup (0.50 ± 0.73 SD) compared to normal metabolizers (0.18 ± 0.44, $p = .006$). We hypothesize that physicians adhering to proscription of CYP2D6-substrate medications will effectively shorten LOS significantly in this subgroup by 1.4 to 2.0 days. By proscribing CYP2D6-substrate drugs in patients with CYP2D6 MR 3.0 or 3.5, we will target another 7.8% of the trial population in whom the trend for increased LOS paralleled a trend toward removal of CYP2D6-substrate drugs. We also observed a trend of a 0.3 day increase in LOS (NS) in 15 patients with highest CYP2D6 MR (3.0, 3.5) and a slightly (though not significantly) increased number of CYP2D6-substrate drugs removed from these patients. Thus we estimate that 40% of the patients will be candidates for proscription of CYP2D6 drugs. In the remaining 60% who are normal metabolizers (MR 1.5, 2.0 or 2.5), CYP2D6-substrate drugs will not be proscribed and no shortening of LOS is hypothesized. The measurable overall effect size on LOS to be detected in *Group G* compared to *Group S* is carried therefore by the 40% of patients with significant metabolic alteration, and is roughly determined as a range:

$$[(0.5\ \textit{days reduced in low MR}) \times (400/1000\ \textit{patients})] + [0\ \textit{days reduced in normal\&high MR} \times (600/1000\ \textit{patients})] = 0.20\ \textit{days}\ \text{through.}$$

$$[(2.0 \text{ days reduced in low MR}) \times (400/1000 \text{ patients})] + [0 \text{ days reduced in normal\&high MR} \times (600/1000 \text{ patients})] = 0.80 \text{ days}$$

We assume standard deviations for LOS of 3.0 days for *Group G* and 4.0 days for *Group S*, which are smaller than the values of 3.1 and 4.77 days, respectively, recorded in the pilot study. The decrease is consistent with that expected with a larger sample size.

3.1.2. Additive genetic model and LOS logarithmic transformation

The genetic modeling is additive with regard to the gene score and the sample size determinations but a log transformation was used for the response. In effect, this is a multiplicative model for the untransformed response, LOS. The CYP2D6 Metabolic Reserve (MR) index represents a series of quantitative phenotypes calculated by adding the functional score of the two *CYP2D6* alleles carried by each patient.

The distribution of LOS can be skewed. If the distribution is not normal, we will normalize it by log transformation or other suitable approach before testing for differences. Log transformation enables us to nearly approach the normal distribution assumptions required by this significance test." Once the logarithmic transformation is effected, the genetic model is additive.

3.1.3. Statistical power projections

Table 2 presents a range of possibilities for statistical power achieved, with sample size estimates of 1000 for *Group G* and 500 for *Group S*, based on a hypothesized range of LOS reduction in patients with low MR, of 0.5 to 2.0 days and the resulting overall impact of this effect on *Group G* vs. *Group S* as a whole. The bold font highlights conditions which are favorable for statistical power of ~80%. Examining a range of LOS reductions of 0.32, 0.44 and 0.57 days, the trial is powered sufficiently to detect an overall reduction between *Group G*

Table 2
Statistical power estimates (1-β) corresponding to a hypothetical range of 0.5 to 2.0 days of LOS reduction in patients with low CYP2D6 MR and 0.32 to 0.58 days LOS reduction for all patients of *Group G*, assuming 1500 patients recruited. See italic text for explanations. Sample size and Power estimates were derived using *nQuery + nTerim 2.0 (2012)*, Sample Size and Power Calculation, "Statsols" (Statistical Solutions Ltd., Cork, Ireland).

Parameter	A	B	C	D	E	F
Difference, **Mean LOS** in ***High MR*** sub-group, μ_G - μ_S	0.0	0.0	0.0	−0.15	−0.15	−0.15
Difference, **Mean LOS** in ***Low MR*** sub-group μ_G - μ_S	−1.0	−1.4	−1.8	−1.8	−1.8	−1.8
Test significance level, α	0.05	0.05	0.05	0.05	0.05	0.05
1 or 2 sided test	2	2	2	2	*1*	2
Mean LOS, μ_G, ALL patients in *Group G*	6.07	5.94	5.81	5.80	5.80	5.80
Mean LOS, μ_S, ALL patients in *Group S*	6.38	6.38	6.38	6.38	6.38	6.38
LOS Reduction (days): Difference in means, μ_G - μ_S	0.31	0.44	0.57	0.58	0.58	0.58
Standard Deviation *Group G*, σ_G	3.0	3.0	3.0	3.0	3.0	2.5
Standard Deviation *Group S*, σ_S	4.0	4.0	4.0	4.0	4.0	3.5
Power (1-β)	34	58	**79**	**81**	**87**	**83**
N_G	1000	1000	1000	1000	*950*	*800*
N_S	500	500	500	500	*475*	*400*

and *Group S* of at least ~0.6 days (14 h) with 1000 patients enrolled for *Group G* and 500 for *Group S* (Columns A-C). The effect of overall LOS reduction attributable to the shortened LOS in high MR patients for *Group G* is negligible owing to the small number of patients expected in the supra-functional category.

In addition, Table 2 (Columns D-F, shaded cells) shows the effects on power attributable to the additional effect of small reductions in LOS for the high MR group, reduced sample sizes, and the use of a one-sided test instead of two sided. By design, we expect *Group G* to experience a shortened LOS. In that case we might resort to a one-sided test for significance. This approach further increases statistical power. For example, whereas the two sided test has 79% power (Column D), the use of the two group Satterthwaite *t*-test with a 0.05 one-sided significance level (Column E) will have 87% power to detect a difference in means of −0.58 (the difference between a *Group G* mean, μ_G, of 5.80 and a *Group S* mean, μ_S, of 6.38) assuming that the *Group G* standard deviation, σ_1, is 3.0 and the *Group S* standard deviation, σ_S, is 4.0 even if there is when the sample sizes are 950 in *Group G* and 475 in *Group S*. For a larger shortfall of 300 patients, there would need to be a reduction in Standard Deviation to retain power (Column F).

3.2. Rate of 30-day readmission

We will track readmission within 30 days as a marker for unsuccessful treatment during the index hospitalization using the same method employed in the preliminary studies. In the pilot study, the overall rate of 30-day readmission was 5.4%. The data in the cohort of 149 patients diagnosed with MDD represent a sample of the IOL inpatient population diagnosed with depression. We will utilize a chi-square test to test for the difference in proportion of patients readmitted to the hospital within 30 days in *all* patients of *Group G* versus *all* patients of *Group S*.

We derive the prediction of a reduced rate of readmission in *Group G* vs. *Group S* based on our previous results across the extremes of CYP2D6 functionality [24]. The combined rate of 30-day readmission of 6/79 (7.6%) in patients with low or high MR was 2.6× higher than the rate in normal metabolizers (2.9%). Some proportion of the higher rate that is seen in the patients on both ends of the CYP2D6 MR distribution can be ascribed to prescribing CYP2D6-substrate drugs which are unsuitable for these patients and causing post hospitalization difficulties contributing to the increased readmission rate.

Assuming that proscription of CYP2D6-substrate drugs during hospitalization will remedy this vulnerability in the sub- and supra-functional patients in *Group G*, we hypothesize that the rate of readmission will be closer to that of the functional patients. We therefore hypothesize a rate of 5% in *Group G* and 10% in *Group S* (Table 3). The overall absolute difference is 5%, which is a large relative effect, a 50% reduction. A two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 92% power to detect the difference between a *Group G* proportion, π_G, of 0.05 and a *Group S* proportion, π_S, of 0.10 (odds ratio of 2.111) when the sample sizes are 1000 and 500, respectively.

Table 3
Statistical power to detect a rate difference of 5% (absolute) in *Group G* vs. *Group S*. Sample size and Power estimates were derived using *nQuery + nTerim 2.0 (2012)*, Sample Size and Power Calculation, "Statsols" (Statistical Solutions Ltd., Cork, Ireland).

Parameter	Value
Test significance level, α	0.05
1 or 2 sided	2
Group G proportion π_G	0.05
Group S proportion π_S	0.10
Odds ratio, $\psi = \pi_S (1-\pi_G) / [\pi_G (1-\pi_S)]$	2.111
Power (1-β)	**92**
N_G	1000
N_S	500
Ratio: N_S / N_G	0.5

4. Discussion

4.1. Design and operations

We carefully considered the implications, including experimental biases, which may result from blinding physicians to a patient's *CYP2D6* genotype results. We considered two plans of implementation. In one, the physicians are informed via CEMS whether the patient is in *Group G* (Genetically guided) arm or in *Group S* (Standard care) arm. Drug guidance based on CYP2D6 functional status is provided for *Group G* patients only. The patient does not know the assignment. In the other, neither patient nor physician knows the group assignment directly. The physician is provided with drug guidance for all patients. In the case of *Group S*, the guidance provided is a chart with all drugs colorized as green, regardless of patient genotype. In the case of *Group G*, drug choices are colorized green, red or yellow depending on the CYP2D6 functionality of the patient, determined by the MR index. We have decided on the later plan. The design has the added reinforcement to the physician that any drugs colorized red or yellow are for patients in *Group G* only, and hence deserving consideration.

Genotyping and functional phenotyping of both the *Group S* and *Group G* patients was introduced to permit cohort genetic stratification. In this manner *Group x CYP2D6 Function Interactions* can also be assessed. Genetic stratification and *Group x Function* interaction was examined. A *Group x Function* matrix could become the format for analysis of the various outcomes. *Group S* could then be considered for analysis of the outcomes in the absence of intervention, and *Group G,* to assess the effect of the therapeutic guidance intervention for sub- and supra-functional patients. The comparison of sub- and supra- functional patients between *Group S* and *Group G* would be particularly informative. The *Group x Function* interaction will also be statistically more powerful to detect genetic effects.

In determining the CYP2D6 functional phenotype from genotype, boundaries need to be defined for categorizations and groupings. We believe that the categories *sub-functional, functional,* and *supra-functional* based on the Metabolic Reserve index elaborated here for the CYP-GUIDES trial are both practical and supported by the allele functional assignments. However, there are evolving efforts in the field needed to harmonize the inferred phenotype from genotype [29]. The extensive database of genotypes that will be collected in the projected 1500 patients in the CYP-GUIDES trial will be a valuable resource in this quest.

The embedded assumption is that determinants other than CYP2D6 functional status will be randomly distributed. Three levels of determinants of hospital length of stay are recognized, including socio-demographic, clinical manifestation, and provider treatment patterns. The data needs to be analyzed by incorporating the effect of various factors such as age, gender, family history, and physician. The variables, all of which may confound LOS, are available in the electronic medical record and would be taken into account as covariates. If randomization is successful, we expect the *Group S* and *Group G* to be balanced with respect to these covariates that are known to be associated with LOS, the primary endpoint.

The implementation is demanding on the institution, as it requires integration of various logistical components in unison, ranging from patient consenting to physician education, from laboratory to informatics. The laboratory expertise in particular is critical because of the molecular complexity *CYP2D6* and the deficient DNA quality of 25% buccal swabs [33]. Expert protocols developed at LPH have enabled genotyping most of these samples, lowering the failure rate to 2–3%. Buccal swabs are preferred in psychiatric settings, as these do not require venipuncture, a great advantage. However, buccal swabs are contaminated with bacterial DNA, which implicates the oral hygiene of

each patient, an issue for the mentally ill.

4.2. Mechanistic considerations of multi-drug regimens

The genetic effect of *CYP2D6* polymorphism is amplified by its interaction with psychotropic exposure during psychiatric hospitalization. There was widespread augmentation of antidepressants with antipsychotics. The majority of inpatients received 2 or more different psychotropics, which are predominantly CYP2D6 dependent. Despite the myriad factors influencing LOS, the immediacy of the *Gene x Drug* interaction is manifested in side effects consequent to non-therapeutic drug levels which may lengthen hospitalization in vulnerable patients. Risk of hospitalization and emergency department visits have been linked to CYP2D6 ultrarapid metabolizer status in a primary care setting [34]. As a variable in clinical research, LOS constitutes a formidably complex phenotype appropriate only for detection of very strong genetic effects.

In this trial, no recommendations are given on dosage because most patients are on multiple drugs. Most of the guidances currently available such as those of the Clinical Pharmacogenetics Implementation Consortium (CPIC) pertain to combinations of individual drugs with genes [35,36]. CPIC has issued valuable guidances for some antidepressants (amitriptyline, citalopram, escitalopram, fluvoxamine, nortriptyline, paroxetine, sertraline). However, guidelines are not available for any of the antipsychotics broadly prescribed in psychiatry. There are no CPIC guidelines for combination therapy of antidepressants and antipsychotics. This void in guidances demonstrates the need and value for a heuristic logic such as the one developed for this trial based on quantitative functional scoring.

In the psychiatric hospital, it would have been difficult to guide dosing of multiple drugs being given to the patient. The pairing of CYP2D6 dependent antidepressants and antipsychotics in this milieu introduces drug interactions that are best managed by substitution and removal of the risky drug by one not dependent on CYP2D6. There will be different psychotrophic drugs used for the treatment of MDD. Clinical outcomes may be affected by differing drugs that physicians order for patients with the same genotype.

Therapeutic drug monitoring (TDM) is not employed in this trial. TDM assesses physiological responses that are pharmacokinetically determined, but requires a separate assay for each drug. Results depend on sample timing and accurate measurement of therapeutic levels and may require multiple samples. Drug levels evidence peaks and troughs dependent on the patient's physiological status. TDM is not feasible due to expense in terms of personnel and methodology. Genotype test result is unchanging and serves as an economical surrogate for pharmacokinetic assessment of the many CYP2D6-substrate drugs.

4.3. Physician behavior

There likely will be systematic physician differences in their delivery of care and disposition toward pharmacogenetic decision support. The effect of genotype-based prescription may not be measured correctly since physicians may elect to override the alert provided by CEMS. The IOL can mandate a response from physicians who override the alert, including why a change was not made, but IOL does not enforce the alert being implemented. We will track whether or not a given alert was responded to before discharge, if responded to when the response occurred (number of days post alert) and type of response (e.g. change in prescription, laboratory test ordered, change in diagnosis). Finally, we also will request brief rationales from physicians on why an alert was not followed (e.g. “patient tolerated and responded to this medicine in the past”).

We expect there will be wide variation, revealing physicians prone to and averse to clinical decision support. Characteristics of the physicians will be tracked as covariates, including years of experience, caseload, and staff status (attending, locum tenens). The research team will work closely with the medical staff for physician education and training on the trial through in-house workshops and Grand Rounds. Depending on the distribution, it may be possible to dichotomize physicians as prone/averse to clinical decision support and compare the drug utilization and length of stay of their patients.

Empirical prescribing is the current standard of care. This practice could be effective on its own, and points out to the need to monitor drug utilization. It will be reflected in a greater number of medications attempted in *Group S* versus *Group G*. Drug utilization represents the best index on implementation of the pharmacogenetic guidance. In subsequent analyses, drug utilization could be used to control for physician compliance, and be introduced as a covariate on LOS.

4.4. Outpatient events

Upon discharge from the hospital, as inpatients transition to outpatient status, alerts do not carry over to the community. There is the chance that community physicians responsible for outpatient pharmacotherapy during the 30 days following discharge may change medications and prescribe a psychotropic proscribed at IOL. This is a potential confounder that nullifies the effect of pharmacogenetic guidance on the 30-day readmission endpoint. In addition, given the low 30-day readmission rate (10%) this endpoint is powered to be detected only if there is a large effect size of the CYP2D6 guidance preserved post-hospitalization.

4.5. Economics and utilization of healthcare resources

The RCT could support a cost benefit analysis for implementation of pharmacogenetics. Assuming 40% of patients to be sub-functional and evidence a length of stay 1–2 days shorter than patients not afforded pharmacogenetic guidance, and projecting a hospitalization cost of $2000–$3000 per day, the savings per patient will be $800–$2400. The return on an investment of ~$500 to genotype could thus range from 0.6 to 3.8 fold. As the cost of genotyping decreases and the number of patients being treated for psychiatric conditions increases, these savings and improvements in quality of care could become increasingly compelling.

Given the controversies surrounding psychiatric biomarkers and their intersection with healthcare policies driving reduction in healthcare costs, the CYP-GUIDES trial has merit in its consideration and implications for health economics. Pharmacogenetics is not only a tool for improved psychiatric patient care, but also for optimization of resource utilization in hospitals.

4.6. Evidence requirements

Biomarkers for personalized medicine should be subject to the same standards of performance and effectiveness as other innovations in healthcare. There is evolving theory and implementation of pharmacogenetic trials [37–39]. Meta-analyses of pharmacogenetics trials and psychiatric remission have shown contradictory evidence [40,41]. In the CYP-GUIDES trial, we utilize formal randomization and blinding to assess *CYP2D6* genotyping and electronic alerts for decision-support versus standard of care for management of psychotropic prescription in hospitalized patients. The RCT design enables the objective assessment of personalized medicine in a high-priority patient population, hospitalized patients diagnosed with major depressive disorder.

The CYP-GUIDES trial for the most important pharmacokinetic gene of psychotropics, *CYP2D6,* applied to inpatient psychiatry is acutely relevant. There is controversy currently about the evidence level for pharmacogenetics in psychiatry [42,43]. Pharmacogenetic models are being scrutizined for the predictive value of each biomarker. This trial addresses this evidence gap and is a model for personalized medicine as a clinical intervention, highlighting the emerging role of genomics in decision support for psychiatry in a rigorous RCT design comparing

genetically-guided versus standard psychotropic prescription.

4.7. Limitations

As a first of its kind, CYP-GUIDES required design simplifications to enable its operations. This pioneering RCT will not consider genes other than *CYP2D6* or its inhibitors. Its guidance concerns prescription and proscription of psychotropics, not dosage recommendations. CYP-GUIDES builds on the results of ongoing work focused on *CYP2D6* at our institution and elsewhere [44,45].

CYP2D6 genetic polymorphism and its consequent functional phenotypes will depend on the affinity of each drug for the CYP2D6 enzyme, which is described by the drug's substrate status (major-, minor-, or non-substrate). The effect is amplified in multi-drug regimens when multiple substrates will be interacting with CYP2D6. For example, we found in our pilot studies at IOL evidence for the widespread psychiatric practice of augmentation of antidepressants with antipsychotics, which are both predominantly CYP2D6 dependent. The co-medications effectively compete for the enzyme, and may reduce the Metabolic Reserve of the patient. Poor and ultra-rapid metabolizer patients represent extreme phenotypes which are least affected by these interactions and drug inhibitors, as these have, respectively, no function to inhibit or excess capacity to retain. Normal metabolizer individuals are the most affected by the interactions, which may then phenocopy poor status. The amount of effective functional reduction due to multiple substrate drugs or inhibitors could be heuristically modeled and will require clinical validation in subsequent trials.

It certainly could be justifiable to include other pharmacokinetic genes (e.g. *CYP2C19, CYP3A4*) in the study, but *CYP2D6* represents the most clinical value based on its dual pharmacokinetic relevance and genetic variability. Most antidepressants and antipsychotropics are primary substrates for the CYP2D6 isoenzyme, and the *CYP2D6* gene is hyperpolymorphic. Only a few antidepressants and none of the antipsychotics are major substrates for CYP2C19. *CYP3A4* is far less polymorphic than *CYP2D6*. Including more genes for clinical decision support does not necessarily mean better actionable guidance. As the roster of genes is increased, so do the possible combinations of alleles that would have to be configured into functional categories and therapeutic guidance. For example, the frequency and relative contribution of each gene combination would have to be modeled and adjudicated in cases of parallel or opposing deficiencies and gains of function. It is for these reasons that *CYP2D6* alone was selected for this initial exploration of genetic guidance for psychotropics as the pharmacokinetic pathway of greatest variability in the population and most clinical importance to antidepressant and antipsychotic prescribing.

Despite these limitations, pilot results have demonstrated that *CYP2D6* genotype status is a significant factor that affects utilization of healthcare resources. The CYP-GUIDES trial and its design rigorously address the fundamental question *"How much does CYP2D6 matter?"* to establish objectively whether the evidence is substantial, suggestive, or inconsequential.

4.8. Reporting and databases

In order to incorporate other pharmacokinetic genes, drug interactions, and dosage recommendations, future clinical research can build on the foundation laid by CYPGUIDES. Results and data from the RCT will become publicly available following guidelines for reporting clinical trials by the funder, Agency for Healthcare Research and Quality. CYP-GUIDES publications and databases will adhere to international standards for transparency such as CONSORT [46] *(Consolidated Standards of Reporting Trials)* or EQUATOR [47] *(Enhancing the Quality and Transparency of Health Research)*.

Acknowledgements

This project was supported by grant number R01HS022304 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

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