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[Intervention Protocol]

Risk assessment for aggressive behaviour in schizophrenia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of aggression or violence risk assessment for people with schizophrenia or schizophrenia-like illnesses.

BACKGROUND

Description of the condition

Schizophrenia

Schizophrenia is a severe mental disorder characterised by distortions of thinking and perception, affecting about 7 per 1000 of the population worldwide (McGrath 2008; WHO 2016a). Schizophrenia typically starts in adolescence or early adulthood (Ballageer 2005; van Os 2009). However, the signs and symptoms of schizophrenia are diverse (Gaebel 2014). Symptoms can be defined as: positive symptoms, which include delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour; negative symptoms such as affective flattening, alogia, or avolition (Tandon 2013); or cognitive symptoms including problems understanding information and using it to make decisions, or trouble focusing or paying attention (NIMH 2009). In order for schizophrenia to be diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), symptoms must be present for one month and supported by indications of social dysfunction at work, school, or interpersonal relationships for at least six months (Tandon 2013).

Schizophrenia affects people worldwide (WHO 2016b). It is a chronic illness with a high disability weight (Whiteford 2013), in part due to other co-existing problems, such as substance misuse, premorbid learning disabilities and developmental disorders (Holloway 2005). These complex problems contribute to major impairments in everyday social functioning, which impede recovery and increase the risk of adverse outcomes. Poor outcomes have been found to be associated with low premorbid functioning or longer duration of unnoticed or untreated psychotic symptoms (Marshall 2005; White 2009).

High mortality rates among people with schizophrenia, which result in a reduction in life expectancy of 10 to 25 years, have been identified (Laursen 2012) and people with schizophrenia are also more likely to be homeless, unemployed, or living in poverty (Eriksson 2011; Maniglio 2009).

Aggressive and violent behaviour

There are no consistent definitions of the terms aggressive or vi-

olent behaviour and in general, these terms refer to "behaviours by one person intended to cause pain, damage, or destruction to another" (Lewis 2009). According to the National Institute for Health and Care Excellence (NICE), aggressive and violent behaviour may be behavioural or verbal (NICE 2015). These behaviours have been linked to people with schizophrenia, and people with psychotic symptoms are often assumed to be violent or aggressive (Nawková 2012; Seeman 2015).

Research into factors associated with inpatient aggressive and violent behaviour has found that, compared to other diagnostic groups, patients with aggressive and violent behaviour are more likely to have schizophrenia or a similar severe mental health disorder, and be hospitalised due to an acute condition (Cornaggia 2011; Edlinger 2014; Fazel 2006; Swanson 2002), but contrary findings exists. For example, in some studies personality disorders and substance abuse have been shown to be the most likely primary diagnoses to be associated with aggressive and violent behaviour (Biancosino 2009; Carr 2008). Other research suggests the factors most frequently associated with aggressive and violent behaviour in psychiatric inpatient care are: a history of past aggressive or violent behaviour, the presence of impulsiveness or hostility, a longer period of hospitalisation, involuntary admission, or the aggressor and victim being of the same gender (Cornaggia 2011). Further findings from a systematic review and meta-analysis indicated that the main factors associated with repeated inpatient aggression or violence were being female, a history of aggression or violence and a history of substance abuse (Dack 2013).

The prevalence of aggressive and violent behaviour in community samples of people with first-episode psychosis has been estimated to vary between 19% (Swanson 2006) and 38% (Coid 2013). Schizophrenia and other psychoses have been associated with community violence and aggression and violent offending, particularly homicide, although most of the excess risk appeared to be mediated by the comorbidity of schizophrenia and substance abuse (Fazel 2009). A recent study further revealed that unique criminal history factors, like a previous conviction for a violent offence, are associated with subsequent violence and aggression for both men and women with schizophrenia (Witt 2015).

The most common problems facing people with schizophrenia in their daily lives, however, are isolation, loneliness, anxiety, and a sense of emptiness, which negatively impact their social life and self-esteem (van Zelst 2009). Problems related to stigma may be worsened by the public perception that people with schizophrenia are aggressive or violent (Torrey 2011). People with schizophrenia themselves are also more likely to be victims (Latalova 2014) of violent and non-violent crimes (Fitzerald 2005).

Aggressive and violent behaviour amongst patients is a challenge for staff working in psychiatric care (Muralidharan 2006). In those thought to be at risk of being aggressive, coercive measures may be used in spite of ethical concerns (Georgieva 2012a). These include the use of a seclusion room (placing the person in a locked isolation room with sensory stimuli reduced) (Mayers 2010), and mechanical/physical restrictions (where devices such as belts are used to restrict a person's free movement) (Hellerstein 2007), physical holding (NICE 2015) and involuntary medication (e.g. intramuscular injection) (Georgieva 2012b). Guidelines recommend that these methods should only be considered if other, less restrictive forms of treatment have failed (APA 2006; Ministry of Health NSW 2012; NICE 2015) and should not be used as preventive measures.

Description of the intervention

Risk assessment for aggressive and violent behaviour has been described extensively in the literature. It has been defined as the process of identifying those who are at the greatest risk of perpetrating violence and aggression (Allnut 2013). Hart 1998 included in his definition that violence risk assessment is "the process of evaluating individuals to characterise the likelihood they will commit acts of violence".

Different methods are used in structured risk assessment. They can be classified as actuarial instruments or structured clinical judgement (NICE 2015; Singh 2011). Actuarial instruments focus on static factors (Quinsey 1998), whereas structured clinical judgement emphasises dynamic risk factors (Almvik 2000) and the strengths and/or protective factors of the patient (Webster 2004). Some risk assessment methods are generally used in clinical settings (NICE 2015) and some are mainly used in research settings (Singh 2011). Risk assessment can focus on the presence or absence of certain characteristics, behaviours or states observed before an incident. These include, for example, a history of alcohol problems, a criminal history, confusion, irritability, verbal threats, physical threats and attacking objects, a negative attitude, social skills and self-care abilities (Almvik 2000; Ogloff 2006; Quinsey 1998; Webster 2004; Yang 2010).

Information regarding patients and their behaviour may be collected by mental health professionals by observing patients' behaviour (Almvik 2000), interviewing patients (Monahan 2000) and carers (Roaldset 2011), or gathering information from patient files (Monahan 2000). These methods are often carried out by nurses (Almvik 2000; Ogloff 2006), psychiatrists (Doyle 2006), psychologists (Monahan 2000), social workers (Monahan 2000), criminologists (Abushua'leh 2006), case managers (van den Brink 2010), researchers (Snowden 2009), the patients themselves (Doyle 2006) or interdisciplinary teams (Webster 2006).

Risk assessment has been used in different populations, contexts and time frames. These methods have been used, for example, in general psychiatry hospitals (Almvik 2000), emergency psychiatry (Skeem 2005) and psychiatric intensive care (Vaaler 2011), psychogeriatric care (Almvik 2007), adolescent psychiatry (Gammelgård 2015), outpatient services (van den Brink 2010) and forensic psychiatry (Dolan 2010). Screening patients for violence and aggression prior to more detailed risk assessment is seen

as important, yet current evidence of the effectiveness of risk assessment for people with schizophrenia is limited (Singh 2011).

How the intervention might work

One of the main purposes of patient risk assessment is prevention (Allnut 2013) or reduction of violence and aggression (NICE 2015). Systematic risk assessment has been recommended as one component of an overall strategy for managing the tendency of patients to be aggressive and violent (Abderhalden 2008). Risk assessment in itself has also been used as an intervention for management of aggressive and violent behaviour (Sival 2000).

Structured risk assessment can be used in psychiatric units as part of routine care. The staff may assess the degree of risk, by assessing a number of specific characteristics, behaviours, signs or states which may occur before aggressive or violent events (e.g. confusion, irritability, boisterousness, verbal threats, physical threats and attacking objects, a negative attitude, impulsivity) (Almvik 2000; Ogloff 2006; Yang 2010). Long-term risk assessment may be used to predict future violent or aggressive acts once the patient re-enters society after being discharged from hospital, and in making decisions concerning patient care or transfer from high-security wards to units with lower security levels (Dolan 2010).

Structured risk assessment may support decision-making processes among health professionals in various ways. By using a list of empirically-supported risk factors, staff may identify behaviours as triggers for upcoming aggressive events, providing them with more time to prepare themselves for the event, or to prevent the event using specific interventions. The assessment can provide some guidance for making decisions on the prevailing situation. In addition, it can offer more in-depth information on a person's current and future situation as well as the intensity and/or the severity of violent or aggressive events (e.g. low, moderate, or high risk of patient violence and aggression) (Schaap 2009; Webster 1997). In order to be effective, patient risk assessment should be integrated into daily clinical practice (Abderhalden 2004).

On the other hand, risk assessment may have disadvantages. These include the unnecessary use of preventive measures (for those with false positive results) (Abderhalden 2004), misallocation of scarce health resources such as the failure to treat the majority of service users with true negative results, the stigmatisation of patients as dangerous (Large 2011), and the focus on risk that could have a negative effect on the therapeutic relationship between health professionals and service users.

Why it is important to do this review

Currently, violence and aggression risk assessment is recommended in the treatment guidelines for violence and aggression prevention in the psychiatric hospital setting (APA 2004; NICE 2014; NICE 2015). Systematic risk assessment approaches may enhance the accuracy of clinical prediction of violent and aggressive outcomes (Dolan 2010). These approaches may also be used for identifying those who are more likely to be at risk of engaging in physically aggressive or violent behaviour (Ogloff 2006) or who are at a high risk of being restrained and secluded (van de Sande 2013). Violence risk assessment may also provide a more humane and safe approach for preventing patients' violent and aggressive behaviour (Georgieva 2012b). In addition, family members could benefit from preventive approaches through an alleviation of the burden and a decrease in the violence or aggression directed towards them (Onwumere 2014). For policy makers, risk assessment could be beneficial in reducing the cost of hospitalisation of violent and aggressive patients (Zhu 2008), and potential expenses caused by injuries and human rights violations could be reduced (Flannery 2011).

However, there is a lack of knowledge as to how effective the various risk assessment approaches are in decreasing aggressive or violent events among patients. It has been assumed (Nijman 1997) that if staff monitor patient behaviour in a standardised way, the monitoring itself may result in a straightforward reduction of violent and aggressive incidents. This is because structured monitoring of patient behaviour keeps staff members more alert and communicative with patients (Nijman 1997). Aggressive or violent behaviour among patients, if not managed, may result in forced medication, seclusion or physical restraints, which are still used in many countries (Raboch 2010). It is therefore important to recognise those patients who may be at risk of being aggressive or violent toward staff members, other patients or their environment (Allnut 2013). This Cochrane systematic review is necessary to examine the evidence for the efficacy of risk assessment for aggressive or violent behaviour in schizophrenia.

OBJECTIVES

To assess the effects of aggression or violence risk assessment for people with schizophrenia or schizophrenia-like illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials will be included. If a trial is described as 'double blind' but implies randomisation, we will include such trials in a sensitivity analysis (see Sensitivity analysis). We will exclude quasi-randomised studies, such as those allocated on alternate days of the week. In studies where people

have been given treatments in addition to risk assessment, we will only include data if the adjunct treatment has been evenly distributed between groups and it is only the aggression or violence risk assessment that has been randomised.

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis. Trials with multiple diagnoses will be included only if the majority of participants have schizophrenia or a related disorder. We will not exclude participants due to age, nationality, gender, duration of illness or treatment setting.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible. We therefore propose, where possible, to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Structured risk assessment and standard professional care

Standard professional care is offered to patients and structured risk assessment (validated or structured clinical judgement) for evaluation of aggressive or violent behaviour among patients is used to predict future aggressive behaviour or decrease violent behaviour.

2. Standard professional care

Standard professional care is offered to patients where no risk assessment (validated or structured clinical judgement) is used to evaluate aggressive or violent behaviour among patients to predict future aggressive or violent events.

Types of outcome measures

We intend to divide outcomes into short-term (less than 3 months), medium-term (3 to 12 months) and long-term (more than 1 year).

Primary outcomes

1. Specific behaviours

1.1 Aggression - clinically important change in aggressive/violent behaviour, as defined by individual studies

Secondary outcomes

1. Use of coercive measures

1.1 Seclusion and restraint
1.1.1 Use of seclusion room (placing a patient in a locked room from which free exit is denied; involves isolation and/or the reduction of sensory stimuli)
1.1.2 Use of mechanical/physical restriction (devices are used to restrict a person's free movement, such as belts/physical holding)
1.2 Additional medication
1.2.1 Use of rapid tranquilisation/increased medication (medication using a parenteral route, if oral medication is not possible or appropriate and urgent sedation with medication is needed)
1.2.2 Use of rapid tranquilisation/increased medication (oral medication for rapid tranquillisation)
1.3 Use of compulsion
1.3.1 Treatment or detainment against will

2. Specific behaviours

2.1 Self harm, including suicide
2.2 Injury to others
2.3 Aggression
2.3.1 Other episode of aggression
2.3.2 Any change in aggression
2.3.3 Average endpoint aggression score
2.3.4 Average change in aggression scores

3. Global state

3.1 Clinically important change global state, as defined by individual studies
3.2 Any change global state
3.3 Relapse
3.4 Average endpoint/change score global state scale

4. Acceptance of treatment

4.1 Accepting treatment
4.2 Average endpoint/change score acceptance scale

5. Satisfaction with treatment

5.1 Clinically important change in satisfaction with treatment (patient or carers), as defined by individual studies
5.2 Any change in satisfaction with treatment (patient or carers), as defined by individual studies

5.3 Average endpoint/change score social satisfaction with treatment scale (patient or carers)

6. Service use

6.1 Admission to hospital
6.2 Duration of stay in hospital
6.3 Rehospitalisation
6.4 Contact with services

7. Adverse effects/event

7.1 Adverse effects - any, as defined by individual studies
7.2 Death - all causes

8. Quality of life

8.1 Clinically important change overall quality of life, as defined by individual studies
8.2 Average endpoint/change score quality of life scale
8.3 Clinically important change in specific aspects of quality of life, as defined by individual studies
8.4 Average endpoint/change score specific aspects of quality of life scale

9. Leaving the study

9.1 For any reason
9.2 For specific reason

10. Costs

10.1 Direct costs
10.2 Indirect costs

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schünemann 2011) and the GRADE profiler (GRADEPRO) to import data from RevMan 5 (Review Manager) to create 'Summary of findings' tables. These tables will provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient care and decision making. We will reportthe following main outcomes in the 'Summary of findings' table:

- Specific behaviours: aggression - clinically important change in aggressive/violent behaviour, as defined by individual studies;
- Use of coercive measure - use of seclusion room;
- Satisfaction with treatment (patient or carers);
- Service use - admission to hospital;
- Adverse effects - any, as defined by individual studies;
- Adverse event - death - all causes;
- Leaving the study early - for any reason.

We aim to use binary data, which are more clinically-meaningful, in the 'Summary of findings' table. If such data are not available we will use relevant continuous data.

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group's Trials Register

The Information Specialist (IS) will search the Cochrane Schizophrenia Group's Study-Based Register of Trials using the following search strategy, which has been developed based on literature review, consulting with the contact author of the review, and checking the indexed interventions in the Group's Register: (*Aggress* OR *Agitat* OR *Impuls* OR *Violen*) in Health Care Condition Field OR (*Aggress* OR *Risk* OR *Seclu* OR *Tranquili* OR *Crisis* OR *Early Intervention* OR *Involunt* OR *Mechanical* *Restrict* OR *Physical* *Restrict* OR *Restrain* OR *Secur* OR *Violen*) in Intervention Field of STUDY The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group Module). There are no language, date, document type, or publication status limitations for inclusion of records into the Register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the included or awaiting assessment studies tables.

Data collection and analysis

Selection of studies

Review authors MV, TL, HH and RK will independently inspect citations from the searches and identify relevant abstracts. SZ will independently re-inspect a random 20% sample to ensure reliability. Where disputes arise, we will acquire the full report for more detailed scrutiny. MV, TL, HH and RK will obtain and inspect full reports of the studies potentially meeting the review criteria. Again, SZ will re-inspect a random 20% of reports in order to ensure reliable selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors MV, TL and RK will extract data from all included studies. In addition, to ensure reliability, SZ will independently extract data from a random sample of these studies, comprising 10% of the total. Again, we will discuss any disagreement, document decisions and, if necessary, we will contact authors of studies for clarification. With remaining problems HH will help clarify issues and we will document these final decisions. We will extract data presented only as graphs and figures whenever possible, but will include these data only if two review authors independently have the same result. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies are multi-centre, where possible, we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto preprepared, standard, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:
a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either be: i. a self-report, or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in the section 'Description of studies' we will note if this is the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We have decided to primarily use endpoint data, and only use change data if the former are not available. We will combine endpoint and change data analysis as we prefer to use mean differences (MD) rather than standardised mean differences (SMD) throughout (Higgins 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aim to apply the following standards.
We will enter skewed data, from studies of at least 200 participants, into the analysis irrespective of the following rules, because skewed data pose less of a problem in large studies. We will also enter change data as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We will present and enter change data into statistical analyses.
For endpoint data:
(a) when a scale starts from the nite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation. If this value is lower than one, it strongly suggests a skew and we will exclude these data. If this ratio is higher than one but below two, there is suggestion of skew. We will enter these data and test whether inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than two we will include these data, because skew is less likely (Altman 1996; Higgins 2011); and
b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), (Kay 1986)) which can have values from 30 to 210), the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and 'S min' is the minimum score.

2.5 Common measure

To facilitate comparison between trials, we intend to convert variables that can be reported in different metrics, such as days in hos-

pital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will try to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for aggression risk assessment instruments. Where keeping to this makes it impossible to avoid outcome titles with clumsy double negatives (e.g. 'Not un-improved') we will report data where the left of the line indicates an unfavourable outcome and make a note in the relevant graphs.

Assessment of risk of bias in included studies

Review authors MV, TL, HH, RK and SZ will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article, in domains such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, we will make the final rating by consensus. Where inadequate details of randomisation and other characteristics of trials are provided, we will contact authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise as to which category a trial is to be allocated, again, we will resolve by discussion. We will note the level of risk of bias in both the text of the review and in the 'Summary of findings' table.

Measures of treatment effect

1. Binary data

For binary outcomes we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The number needed to treat for an additional beneficial/harmful outcome(NNTB/H) statistic with its CIs is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, where possible, we will calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes we aim to estimate the mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate effect size and transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

We have received statistical advice that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported we will assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the

second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, the additional treatment arms will be presented in comparisons. If data are binary we will simply add these and combine within the two-by-two table. If data are continuous we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms are not relevant, we will not use these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). If for any particular outcome, more than 50% of data are unaccounted for, we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table/s by downgrading quality. We will also downgrade quality within the 'Summary of findings' table/s if the loss is 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0 and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes we will use the rate of those who stayed in the study - in that particular arm of the trial - for those who did not. We will undertake a sensitivity analysis testing how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome is between 0 and 50%, and data only from people who complete the study to that point are reported, we will reproduce these data.

3.2 Standard deviations

If standard deviations (SDs) are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error and CIs available for group means, and either P value or 't' value available for differences in mean, we can calculate them according to the following rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When only the standard error (SE) is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) present detailed formula for estimating SDs from P values, t or F values, CIs, ranges or other statistics. If these formula do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless will examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently, methods such as multiple imputation or mixed effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, we will preferably use the more sophisticated approaches; that is, MMRM or multiple imputation will be preferred to LOCF, and completer analyses will only be presented if some kind of intention-to-treat data are not available at all. Moreover, we will address this issue in the item "incomplete outcome data" of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for clearly outlying people or situations which we had not predicted would arise. We will fully discuss such situations or participant groups when they arise.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise. We will discuss such methodological outliers when they arise.

3. Statistical heterogeneity

3.1 Visual inspection

We will visually inspect graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on: i. magnitude and direction of effects, and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for I^2). We will interpret an I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic as evidence of substantial levels of heterogeneity (section 9.5.2, Higgins 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for this heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report. If the protocol is not available, we will compare outcomes listed in the methods section of the trial report with the results actually reported.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are ten or fewer studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preferring the use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased. Depending on the direction of effect these studies can either inflate or deflate the effect size. We will use a fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

No subgroup analysis are anticipated.

1.2 Clinical state, stage or problem

We will provide an overview of the effects of aggression risk assessment instruments for people with schizophrenia in general. In addition, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

We will report if inconsistency is high. First we will investigate whether data have been entered correctly. Second, if data are correct, we will visually inspect the graph and successively remove studies outside of the company of the rest to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we will present these data.

If not, we will not pool data and will discuss any relevant issues. We know of no supporting research for this 10% cut off but are investigating the use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity are obvious we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

We aim to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes we will include these studies and if there is no substantive difference when the implied randomised studies are added to those with better description of randomisation, then we will employ all useable data from these studies. If their inclusion does result in important clinically-significant but not necessarily statistically-significant differences, we will present such data within a subcategory, rather than adding the data from lower quality studies to the results of higher quality trials.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see Dealing with missing data) we will compare the findings of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption.

Where assumptions have to be made regarding missing SDs (see Dealing with missing data), we will compare the findings of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. We will undertake a sensitivity analysis testing how prone results are to change when completer-only data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias does not substantially alter the direction of effect or the precision of the effect estimates, we will include data from these trials.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials.

If substantial differences are noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome, but will present them separately.

5. Fixed-effect and random-effects

All data will be synthesised using a fixed-effect model, however, we will also synthesise data for the primary outcome using a random-effects model to evaluate whether this alters the significance of the results.

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

MV - initiation of the review, development and writing of protocol.

TL - development and writing of protocol.

HH - development and writing of protocol.

RK - development and writing of protocol.

SZ - development and writing of protocol.

DECLARATIONS OF INTEREST

MV - has completed studies about patient aggression.

TL - has completed studies about patient aggression.

HH - has completed studies about patient aggression.

RK - has completed studies about patient aggression.

SZ - None known.

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