Cochrane Library

Cochrane Database of Systematic Reviews

Video games for schizophrenia (Protocol)

Lloyd J, Välimäki M, Ho GW

Lloyd J, Välimäki M, Ho GW.
Video games for schizophrenia.
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012844.
DOI: 10.1002/14651858.CD012844.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Video games for schizophrenia

Jack Lloyd[1], Maritta Välimäki[2,3,4], Grace W.K. Ho[2]

[1]Royal Derby Hospital Medical School, Medical Physiology and Therapeutics, Nottingham, UK. [2]School of Nursing, The Hong Kong Polytechnic University, Hong Kong, China. [3]Department of Nursing Science, University of Turku, Turku, Finland. [4]Turku University Hospital, Turku, Finland

Contact address: Jack Lloyd, Royal Derby Hospital Medical School, Medical Physiology and Therapeutics, 35 Johnson Road, Nottingham, UK. mzyjwl@nottingham.ac.uk, jacklloyd1033@gmail.com.

Editorial group: Cochrane Schizophrenia Group.
Publication status and date: New, published in Issue 10, 2017.

Citation: Lloyd J, Välimäki M, Ho GW. Video games for schizophrenia. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No.: CD012844. DOI: 10.1002/14651858.CD012844.

ABSTRACT

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

To review the effects of video games as a comparison for standard care or other interventions including, but not limited to, cognitive remediation or cognitive behavioural therapy for people with schizophrenia or schizophrenia-like illnesses.

BACKGROUND

Description of the condition

Schizophrenia is a psychiatric disorder that affects populations worldwide (Owen 2016). It is estimated that the median incidence for schizophrenia is 15.2 in every 100,000 people, with a prevalence ratio for males:females of 1.4:1 (McGrath 2008). Typical age of onset is late adolescence, which is the time when brain development can be susceptible to onset and development of psychosis (Gogtay 2011).

Compared with the general population, people with schizophrenia have a two- to three-fold higher mortality rate, which translates to a 10- to 25-year life expectancy reduction (Laursen 2012). Suicide is the most common cause of premature death for people with schizophrenia, with a meta-analysis estimation that 4.9% of people with schizophrenia will commit suicide during their lifetime (Palmer 2005). Whereas generally, a lifetime prevalence cross-nationally of suicide attempts in the general population is 2.7% (Nock 2008).

People with schizophrenia experience an array of symptoms. The 13 core symptoms can be grouped into five broad categories: 1. positive symptoms (delusion, unusual thought content, hallucinations), 2. negative symptoms (flat affect, emotional withdrawal, self-neglect, impaired motivation), 3. depressive symptoms (depressive mood, anxiety), 4. cognitive symptoms (lack of attention, disorientation) and 5. behavioural symptoms (hostility, euphoria) (Bak 2001).

Antipsychotic medication is the mainstay treatment for the symptoms of schizophrenia and these medications tend to have a beneficial effect on managing positive symptoms such as delusions, unusual thoughts and hallucinations (Suenderhauf 2016). However, negative symptoms, such as anhedonia and social withdrawal, are usually more difficult to manage (Suenderhauf 2016). The number of people with chronic schizophrenia who do not get an adequate response with medication is around 50% to 60% (Yang 2015). As a result, people with schizophrenia continue to experi-

ence distressing, chronic symptoms (Bauer 2011).
Other interventions, such as cognitive remediation, are often used as an adjunctive treatment to antipsychotic drugs, incorporating computerised exercises to improve cognitive processes in people with schizophrenia (Barlati 2013). Video games, while also being a form of computerised exercises, have also been linked to cognitive benefits (Granic 2014).

Description of the intervention

We will define video gaming as *computerised, electronic manipulation* of images forming an *interactive, graphically interesting* game played using a controller or keyboard on a display monitor. Video gaming is now one of the most popular recreational pastimes (Wittek 2016), and it differs to other similar forms of recreational pastimes such as reading books and watching television due to their interactive elements. Players are not forced to adhere to a game's storyline, they are actively involved in the development of the game and, in turn, the game actively responds to the players' behaviour (Granic 2014). Games can be played alone, competitively against another person or with people worldwide using online platforms. Games can be played using consoles (e.g. Xbox, Playstation), computers or even mobile phones (Granic 2014). This is the largest entertainment industry in the UK (Hollingdale 2014), and 25% of Europeans play games at least once a week (Ipsos MediaCT 2012) and 59% of North Americans (Ipsos MediaCT 2014). Being a constantly improving technology, using serious games for training and educational purposes is also a burgeoning area. In people with psychosis, these types of games greatly improve the adherence to e-interventions (O'Hanlon 2016). The games incorporate 'rewards' or 'extra lives' that can be redeemed daily, thus encouraging much needed engagement with services (O'Hanlon 2016). This improvement in adherence is not surprising given that by 21 years of age, the average adolescent is estimated to have played around 10,000 hours of video games (Kuhn 2014).

How the intervention might work

Many people believe that playing video games promotes intellectual laziness (Granic 2014) and sedentary lifestyles (Hernandez 1999; Owen 2010), which are highly prevalent in people with schizophrenia (Kimhy 2016). In the same vein, they can be detrimental to public health due to increased aggression of players (Hollingdale 2014). On the contrary, it has been found that these games allow players to develop a wide range of cognitive skills (Granic 2014). Behavioural and magnetic resonance imaging studies have demonstrated that video games have the potential to impact brain plasticity (Suenderhauf 2016). Video games are easily accessible and can counteract the limitations of other therapies (e.g. cognitive behavioural therapy). These include a reduction in the number of clinicians properly trained in the approach, limited patient resources and people choosing not to access mental health services. About 50% of people with schizophrenia in the USA do not receive any treatment (Gottlieb 2013). Video games can potentially offer relief for people with schizophrenia without the need for professionals and entice a larger amount of the population to engage with services. Further, people with schizophrenia have shown a reduction in delusional thinking and extrapyramidal symptoms following only eight weeks of Internet-game play (Bavelier 2011).
One way in which video games may be beneficial in treating people with schizophrenia is through distraction, that is, the holding or focusing of attention (Trygstad 2002). Due to the suspenseful and pleasurable nature of video games, they have the potential to fully engage a player's attention (Suenderhauf 2016). We will define distraction as a 'real-life' action *voluntarily* taken, which then increases vulnerability to the *involuntary* distraction from symptoms.
The largest problem faced by clinicians is engagement with young people and adolescents. This may be due to young people and adolescents not engaging with the therapies or not recognising they have a mental health problem (Granic 2014). Video games not only have the ability to engage adolescents, but also the wider population. In the UK, 37% of the population aged 16 to 49 years described themselves as 'active gamers' (Morris 2013). Further, an age breakdown of gamers on average across Europe sees 51% below 35 years of age and 49% above years of age (Ipsos MediaCT 2012). As well as distraction from symptoms, video gaming also increases positive attitudes, improves problem solving and eliminates abnormal behaviours (Fernandez-Aranda 2012).
Video games, stereotypically, are perceived to be a static activity. However, there are now games called 'exergames' that are video games that look to promote physical fitness and rehabilitate motor function in various populations. These games allow play while incorporating exercise as the game responds to bodily movements. Physical activity is reduced in people with schizophrenia and 'exergames' improve endurance, motor co-ordination, flexibility and balance skills so they could become a robust intervention for people with schizophrenia (Campos 2015).
Due to a growing interest from several healthcare systems in increasing accessibility of treatment for mental health disorders, implementing these new technologies to treat people with schizophrenia is something that is desired by many (Fernandez-Aranda 2012). If video gaming could be used successfully to provide targeted functional activation changes, it could regarded as a robust intervention for people with severe psychiatric disorders such as schizophrenia. With the majority of the games being targeted at young people, this could provide an added benefit, as it is consistent with late adolescence, which is the typical age of onset of schizophrenia (Gogtay 2011).

Why it is important to do this review

We are unsure if commercial games have an effect on the mental well-being of people in general and of people with schizophrenia in particular. There is concern that they could be detrimental (Tortolero 2014). Notwithstanding, video gaming has not only shown possible physiological benefits but also a much needed improvement with engagement of services in people with psychosis (O'Hanlon 2016). However, we are also aware that they can be used as an easy control group to more sophisticated - and expensive - interventions such as cognitive remediation. Much as with another Cochrane Review assessing supportive therapy for people with schizophrenia (Buckley 2015), the low-grade 'control' to many more complex approaches are the main focus of this review. If, as for the *Supportive therapy for schizophrenia* review (Buckley 2015), the control intervention is as effective as the more expensive approaches, simple commercial computer games could save an enormous waste of finite resources on researching ostensibly convincing, but ultimately ineffective, interventions.

OBJECTIVES

To review the effects of video games as a comparison for standard care or other interventions including, but not limited to, cognitive remediation or cognitive behavioural therapy for people with schizophrenia or schizophrenia-like illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) meeting our inclusion criteria and reporting useable data. We will consider trials that are described as 'double blind' - in which randomisation is implied - and include or exclude them once we have carried out a sensitivity analysis (see Sensitivity analysis). We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week. Where people were given other treatments in addition to video games, we will only include the studies if the adjunct treatment is evenly distributed between groups.

Types of participants

Adults, however defined, with schizophrenia or schizophrenia-like illnesses, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis. We will include trials that include adolescents (aged over 16 years) with schizophrenia or related disorders alongside adults with schizophrenia. However, we will exclude any trial that involves 'young people at risk of psychosis' as these people do not have psychosis.

We are interested in ensuring that information is relevant to the current care of people with schizophrenia, so aim to highlight the current clinical state clearly (acute, early postacute, partial remission, remission), the stage (prodromal, first episode, early illness, persistent), and whether the studies primarily focused on people with particular problems (e.g. negative symptoms, treatment-resistant illnesses).

Types of interventions

We will compare video games versus standard care alone or other psychological treatments.

1. Video games

We are interested in using commercial video games, played alone, co-operatively or competitively, using a console (e.g. Xbox, Playstation), computer or mobile phone. To be considered 'video gaming,' the games will include an interactive element. The players will not have to adhere to a set storyline, but they must be actively engaged in the development of the story, and the computer game in turn will respond to the player's behaviour (Granic 2014).

We will include any intervention that calls itself a 'video' or 'computer' game. Additionally, we will include 'exergames' as a form of computer game if the game is interactive and responds to the player's actions. However, we will not include virtual reality as a form of video gaming as this will be the focus of another review.

We envisage that the video games will be given alongside the standard professional care that people with schizophrenia would receive.

2. Standard care alone

The standard care that the person normally receives had they not participated in the trial. These will include, but will not be limited to, medication and hospitalisation.

3. Other psychological treatments

Including, but not limited to, cognitive behavioural therapy, cognitive remediation, psychodynamic psychotherapy or problem-solving therapy.

Types of outcome measures

We will divide all outcomes into short term (less than six months), medium term (six to 12 months) and long term (over 12 months). We will endeavour to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a rating

scale defined within the trials). Thereafter, we will list other binary outcomes and then those that are continuous.

Primary outcomes

1. Functioning

1.1 General: clinically important change in general functioning - as defined by study, including working ability.
1.2 Cognitive: clinically important change in cognitive functioning - as defined by study.
1.3 Social: clinically important change in social functioning - as defined by study.

2. Adverse effects

2.1 At least one important adverse effect.

Secondary outcomes

1. Functioning

1.1 General: any change in general functioning - as defined by study, including working ability.
1.2 Cognitive: any change in cognitive functioning - as defined by study.
1.3 Social: mean endpoint or change score on social functioning scale.
1.4 Social: any change in social functioning - as defined by study e.g. social skills.

2. Adverse effects

2.1 Any change in adverse effects: general/specific.
2.2 Very serious event (e.g. death, serious self-harm, suicide).
2.3 Any change in specific adverse effects (e.g. repetitive strain injury, aggression).

3. Mental state

3.1 Clinically important change in general mental state - as defined by study.
3.2 Mean endpoint or change score on general mental state scale.
3.3 Clinically important change in specific symptoms - as defined by study (positive, negative, affective, cognitive symptoms of schizophrenia).

4. Physical fitness

4.1 Clinically important change in overall physical fitness - as defined by study.
4.2 Mean change score in overall physical fitness.
4.3. Clinically important change in specific aspects of physical fitness - as defined by study.
4.4. Mean change scores in specific aspects of physical fitness.

5. Global state

5.1 Clinically important change in global state (clinical response as defined by study, e.g. global impression of much improved, or more than 50% improvement on a rating scale).
5.2.Relapse - as defined by study.
5.3.Mean endpoint or change score on general global state scale.

6. Leaving the study early

6.1 For any reason.
6.2 Due to inefficacy.
6.3 Due to adverse effect.

7. Quality of life

7.1 Any change in quality of life - as defined by study.
7.2 Mean endpoint or change score on quality of life scale.
7.3 Any change in specific aspects of quality of life - as defined by study.
7.4 Mean endpoint or change score on specific aspects of quality of life scale.

8. Behaviour

8.1 Any change in general behaviour - as defined by study.
8.2 Mean endpoint or change score general behaviour scale.
8.3 Any change in specific aspects of behaviour - as defined by study (e.g. aggression, violence).
8.4. Mean endpoint or change on specific aspects of behaviour scale.

9. Economic outcomes

9.1 Costs due to treatment, as defined by study.
9.2 Total direct and indirect costs.
9.3 Mean change in total cost of medical and mental health care.

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schünemann 2011); and will use GRADEpro GDT to export data from our review to create a 'Summary of findings' table. These tables provide outcome-specific information concerning the overall

certainty 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 select the following main outcomes for inclusion in the 'Summary of findings' table:

1. Functioning - General: clinically important change in general functioning - as defined by study, including working ability.
2. Functioning - Cognitive: clinically important change in cognitive functioning - as defined by study.
3. Functioning - Social: clinically important change in social functioning - as defined by study.
4. Adverse effect: at least one important adverse effect.
5. Mental state: clinically important change in general mental state - as defined by study.
6. Physical fitness: clinically important change in physical fitness - as defined by study.
7. Quality of life: any change in quality of life - as defined by study.

If data are not available for these prespecified outcomes but are available for ones that are similar, we will present the closest outcome available, but take this into account when grading the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The information specialist will search the register using the following search strategy:

Game in Intervention Field of STUDY

In such study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017).

This register is compiled by systematic searches of major resources (AMED, BIOSIS, CINAHL, ClinicalTrials.Gov, EMBASE, MEDLINE, PsycINFO, PubMed, and WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, hand-searches, grey literature, and conference proceedings (see Group's Module). There is 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 studies' or 'Studies awaiting classification' tables.

Data collection and analysis

Selection of studies

Review authors (JL, GH) will independently inspect citations from the searches and identify relevant abstracts; MV will independently reinspect a random 20% sample of these abstracts to ensure reliability of selection. Where disputes arise, we will acquire the full report for more detailed scrutiny. Review authors JL and GH will then obtain and inspect full reports of the abstracts or reports meeting the review criteria. MV will re-inspect a random 20% of these full reports to ensure reliability of selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study concerned for clarification.

Data extraction and management

1. Extraction

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

2. Management

2.1. Forms

We will extract data onto standard, pre-designed, simple forms.

2.2. Scale-derived data

We will include continuous data from rating scales only if:

1. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
2. the measuring instrument has not been written or modified by one of the trialists for that particular trial;
3. the instrument should be a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable. However, there are exceptions, we will include subscores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally the measuring instrument should either be a self-report or completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in '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; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We will primarily use endpoint data, and only use change data if the endpoint data are not available. If necessary, we will combine endpoint and change data in the analysis, as we prefer to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Deeks 2011).

2.4. Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the problems of applying parametric tests to non-parametric data, we will apply the following standards to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants:

1. 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 (SD). If this value is lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher than one but less than two, there is suggestion that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than two, we will include these data, because it is less likely that they are skewed (Altman 1996; Higgins 2011);
2. if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we will modify the calculation described above to take the scale starting point into account. In these cases, skewed data are present if 2 SD > (S - S_{min}), where S is the mean score and S_{min} is the minimum score.

Please note: we will enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant 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 determine whether data are skewed.

2.5. Common measurement

To facilitate comparison between trials, we will, where relevant, convert variables that can be reported in different metrics, such as days in hospital (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 2005; Leucht 2005a). 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 so that the area to the left of the line of no effect indicates a favourable outcome for video games. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved'), we will report data where the left of the line indicates an unfavourable outcome and note this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors (JL, GH) will independently assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011a). This set of criteria is based on evidence of associations between potential overestimation of effect and the level of risk of bias of the

article that may be due to aspects of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, or the way in which these 'domains' are reported.
If the raters disagree, we will make the final rating by consensus, with the involvement of MV. Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact authors of the studies to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise regarding the category to which a trial is to be allocated, we will resolve this by discussion.
We will note the level of risk of bias in the text of the review, 'Risk of bias' graph, 'Risk of bias' summary, and the 'Summary of findings' table/s.

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), as it has been shown that RR is more intuitive than odds ratios (Boissel 1999); and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, we will, where possible, calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes, we will estimate MD between groups. We prefer not to calculate effect size measures (SMD). However, if scales of very 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. Authors often fail to account for intraclass correlation in clustered studies, leading to a unit-of-analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; 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.
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 intraclass correlation coefficients (ICC) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).
We have sought statistical advice and have been advised that the binary data from cluster trials 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: thus, 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 and taken ICCs and relevant data documented in the report into account, 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. This 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, participants can differ significantly from their initial state at entry to the second phase, despite a washout phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions 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, we will present the additional treatment arms 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 the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where additional treatment arms are not relevant, we will not reproduce 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). We choose that, for any particular outcome, should more than 50% of data be unaccounted for we will not reproduce these data or use them within analyses. However, if more than 50% of participants 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 down-grading quality. Finally, we will also downgrade quality within the 'Summary of findings' table/s should the loss be 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 (ITT) analysis). Participants leaving the study early are all assumed to have the same rates of negative outcome as participants who completed, with the exception of the outcome of death and adverse effects. For these outcomes, the rate of participants who stay in the study (in that particular arm of the trial) will be used for participants 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 ITT analysis using the above assumptions.

3. Continuous

3.1. Attrition

We will use data 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.

3.2. Standard deviations

If SDs are not reported, we will try to obtain the missing values from the authors. If these are not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we can calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When only the SE is reported, SDs are calculated by the formula SD = SE × $\sqrt{}$(n). The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values; CIs; ranges or other statistics (Higgins 2011). If these formulae 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. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis that excludes 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; other trials 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 multiple imputation or mixed-effects model methods seem to be somewhat better than LOCF (Leon 2006), we consider that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in randomised schizophrenia trials. Therefore, we will not exclude studies based on the statistical approach used. However, by preference, we will use the more sophisticated approaches, that is, we will prefer to use MMRM or multiple-imputation to LOCF, and we will only present completer analyses if some type of ITT 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 participants who are clearly outliers or situations that we had not predicted would arise and, where found, discuss such situations or participant groups.

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 and discuss any such methodological outliers.

3. Statistical heterogeneity

3.1. Visual inspection

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

3.2. Employing the I² statistic

We will investigate heterogeneity between studies by considering the I² statistic alongside the Chi² P value. The I² statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of the I² statistic depends on the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P value from Chi² test, or a CI for the I² statistic). We will interpret an I² statistic estimate of 50% or greater and accompanied by a statistically significant Chi² statistic as evidence of substantial heterogeneity (Chapter 9, *Cochrane Handbook for Systematic Reviews of Interventions*; Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 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 10 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 preference for 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. However, there is a disadvantage to the random-effects model as it puts added weight onto small studies, which often are the most biased studies. 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

We are unlikely to conduct a subgroup analysis as we do not anticipate sufficient power to carry it out.

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 inspect the graph visually and remove outlying studies successively 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 10% of the total weighting, we will present data. If not, we will not pool these data and will discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is 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 that implies randomisation. For primary outcomes, if the inclusion of these trials does not result in a substantive difference, they will remain in the analyses. If their inclusion does result in clinical, but not necessarily statistically significant differences, we will not add the data from these lower-quality studies to the results of the higher-quality trials, but will present these data within a subcategory.

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 compared with completer data only. If there is a substantial difference, we will report results and discuss them, but continue to employ our assumption.

Where assumptions have to be made regarding missing SD data (see Dealing with missing data), we will compare the findings of primary outcomes when we use our assumption compared with complete data only. We will undertake a sensitivity analysis to test how prone results are to change when completer 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 continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are at high risk of bias across one or more of the 'Risk of bias' domains (see Assessment of risk of bias in included studies) for the meta-analysis

of the primary outcomes. If the exclusion of trials at high risk of bias does not alter the direction of effect or the precision of the effect estimates substantially, then we will include relevant data from these trials.

4. Imputed values

We will undertake a sensitivity analysis to assess the effects of including data from trials where we use imputed values for ICC in calculating the design effect in cluster-randomised trials.
If there are substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses, 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 models

We will synthesise data using a fixed-effect model; however, we will also synthesise data for the primary outcomes using random-effect model to evaluate whether this alters the significance of the results.

ACKNOWLEDGEMENTS

The Cochrane Schizophrenia Group Editorial Base at The University of Nottingham, Nottingham, UK, produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis for this protocol and adapted it as required.

We would like to thank Victoria Bird, Maya Seegers and Ambrish Singh for peer reviewing this protocol.

We wish to acknowledge Clive Adams for his support with the protocol.

REFERENCES

Additional references

Altman 1996
Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**(7066):1200.

Bak 2001
Bak M, van der Spil F, Gunther N, Radstake S, Delespaul P, van Os J. Maastricht Assessment of Coping Strategies (MACS-I): a brief instrument to assess coping with psychotic symptoms. *Acta Psychiatrica Scandinavica* 2001; **103**(6):453–9. [PUBMED: 11401660]

Barlati 2013
Barlati S, Deste G, De Peri L, Ariu C, Vita A. Cognitive remediation in schizophrenia: current status and future perspectives. *Schizophrenia Research and Treatment* 2013; **2013**:156084. [PUBMED: 24455253]

Bauer 2011
Bauer SM, Schanda H, Karakula H, Olajossy-Hilkesberger L, Rudaleviciene P, Okribelashvili N, et al. Culture and the prevalence of hallucinations in schizophrenia. *Comprehensive Psychiatry* 2011;**52**(3):319–25. [PUBMED: 21497227]

Bavelier 2011
Bavelier D, Green CS, Han DH, Renshaw PF, Merzenich MM, Gentile DA. Brains on video games. Nature Reviews. Neuroscience 2011; Vol. 12, issue 12:763–8. [PUBMED: 22095065]

Bland 1997
Bland JM. Statistics notes. Trials randomised in clusters. *BMJ* 1997;**315**(7108):600.

Boissel 1999
Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, et al. The problem of therapeutic efficacy indices. 3. Comparison of the indices and their use [Aperçu sur la problématique des indices d'efficacité thérapeutique, 3: comparaison des indices et utilisation. Groupe d'Etude des Indices D'efficacite]. *Therapie* 1999;**54**(4):405–11. [PUBMED: 10667106]

Buckley 2015
Buckley LA, Maayan N, Soares-Weiser K, Adams CE. Supportive therapy for schizophrenia. *Cochrane Database of Systematic Reviews* 2015, Issue 4. [DOI: 10.1002/14651858.CD004716.pub4; CD004716

Campos 2015
Campos C, Mesquita F, Marques A. Feasibility and acceptability of an exergame intervention for schizophrenia. Psychology of Sport and Exercise 2015; Vol. 19:50–8.

Deeks 2000
Deeks J. Issues in the selection for meta-analyses of binary data. 8th International Cochrane Colloquium; 2000 Oct 25-28; Cape Town, South Africa. Cape Town (South Africa): The Cochrane Collaboration, 2000.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Divine 1992
Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623–9.

Donner 2002
Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**(19): 2971–80.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Elbourne 2002
Elbourne D, Altman DG, Higgins JPT, Curtina F, Worthingtond HV, Vaile A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Fernandez-Aranda 2012
Fernandez-Aranda F, Jimenez-Murcia S, Santamaria JJ, Gunnard K, Soto A, Kalapanidas E, et al. Video games as a complementary therapy tool in mental disorders: PlayMancer, a European multicentre study. *Journal of Mental Health (Abingdon, England)* 2012;**21**(4):364–74. [PUBMED: 22548300]

Furukawa 2006
Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(1):7–10.

Gogtay 2011
Gogtay N, Vyas NS, Testa R, Wood SJ, Pantelis C. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. *Schizophrenia Bulletin* 2011;**37**(3): 504–13. [PUBMED: 21505117]

Gottlieb 2013
Gottlieb JD, Romeo KH, Penn DL, Mueser KT, Chiko BP. Web-based cognitive-behavioral therapy for auditory hallucinations in persons with psychosis: a pilot study. *Schizophrenia Research* 2013;**145**(1-3):82–7. [PUBMED: 23410709]

Granic 2014
Granic I, Lobel A, Engels RC. The benefits of playing video games. *American Psychologist* 2014;**69**(1):66–78. [PUBMED: 24295515]

Gulliford 1999
Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology* 1999;**149** (9):876–83.

Hernandez 1999
Hernandez B, Gortmaker SL, Colditz GA, Peterson KE, Laird NM, Parra-Cabrera S. Association of obesity with physical activity, television programs and other forms of video viewing among children in Mexico city. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 1999;**23** (8):845–54. [PUBMED: 10490786]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JPT, Green S. Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011a
Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hollingdale 2014
Hollingdale J, Greitemeyer T. The effect of online violent video games on levels of aggression. *PloS One* 2014;**9**(11): e111790. [PUBMED: 25391143]

Hutton 2009
Hutton JL. Number needed to treat and number needed to harm are not the best way to report and assess the results of randomised clinical trials. *British Journal of Haematology* 2009;**146**(1):27–30. [PUBMED: 19438480]

Ipsos MediaCT 2012
Ipsos MediaCT. Videogames in Europe: Consumer study, 2012. www.isfe.eu/sites/isfe.eu/files/attachments/euro_summary_-_isfe_consumer_study.pdf (accessed prior to 9 October 2017).

Ipsos MediaCT 2014
Ipsos MediaCT. The 2014 essential facts about the computer and video game industry, 2014. www.theesa.com/wp-content/uploads/2014/10/ESA_EF_2014.pdf (accessed prior to 9 October 2017).

Kay 1986
Kay SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) Manual*. North Tonawanda (NY): Multi-Health Systems, 1986.

Kimhy 2016
Kimhy D, Khan S, Ayanrouh L, Chang RW, Hansen MC, Lister A, et al. Use of active-play video games to enhance aerobic fitness in schizophrenia: feasibility, safety, and adherence. *Psychiatric Services (Washington, D.C.)* 2016;**67** (2):240–3. [PUBMED: 26423100]

Kuhn 2014
Kuhn S, Gleich T, Lorenz RC, Lindenberger U, Gallinat J. Playing Super Mario induces structural brain plasticity: gray matter changes resulting from training with a commercial video game. *Molecular Psychiatry* 2014;**19**(2):265–71. [PUBMED: 24166407]

Laursen 2012
Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current Opinion in Psychiatry* 2012;**25**(2): 83–8. [PUBMED: 22249081]

Leon 2006
Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biological Psychiatry* 2006;**59**(11): 1001–5. [PUBMED: 16905632]

Leucht 2005
Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean?. *Schizophrenia Research* 2005;**79**(2-3):231–8. [PUBMED: 15982856]

Leucht 2005a
Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. Clinical implications of Brief Psychiatric Rating Scale scores. *British Journal of Psychiatry* 2005;**187**:366–71. [PUBMED: 16199797]

Marshall 2000
Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**: 249–52.

McGrath 2008
McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews* 2008;**30**:67–76. [PUBMED: 18480098]

Morris 2013
Morris G, Forrest R. Wham, sock, kapow! Can Batman defeat his biggest foe yet and combat mental health discrimination? An exploration of the video games industry and its potential for health promotion. *Journal of Psychiatric and Mental Health Nursing* 2013;**20**(8):752–60. [PUBMED: 23964592]

Nock 2008
Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *British Journal of Psychiatry* 2008;**192**(2):98–105. [PUBMED: 18245022]

O'Hanlon 2016
O'Hanlon P, Aref-Adib G, Fonseca A, Lloyd-Evans B, Osborn D, Johnson S. Tomorrow's world: current developments in the therapeutic use of technology for psychosis. BJPsych Advances 2016; Vol. 22, issue 5: 301–10.

Overall 1962
Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychological Reports* 1962;**10**:799–812.

Owen 2010
Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging evidence for a new health risk. *Mayo Clinic proceedings* 2010;**85**(12):1138–41. [PUBMED: 21123641]

Owen 2016
Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet* 2016;**388**(10039):86–97. [PUBMED: 26777917]

Palmer 2005
Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Archives of General Psychiatry* 2005;**62**(3):247–53. [PUBMED: 15753237]

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Shokraneh 2017
Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. *BioImpacts* 2017; **InPress**:InPress.

Sterne 2011
Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editor (s). Cochrane Handbook for Systematic Reviews of Intervention Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Suenderhauf 2016
Suenderhauf C, Walter A, Lenz C, Lang UE, Borgwardt S. Counter striking psychosis: commercial video games as potential treatment in schizophrenia? A systematic review of neuroimaging studies. *Neuroscience and Biobehavioral Reviews* 2016;**68**:20–36. [PUBMED: 27090742]

Tortolero 2014
Tortolero SR, Peskin MF, Baumler ER, Cuccaro PM, Elliott MN, Davies SL, et al. Daily violent video game playing and depression in preadolescent youth. *Cyberpsychology, Behavior and Social Networking* 2014;**17**(9):609–15. [PUBMED: 25007237]

Trygstad 2002
Trygstad L, Buccheri R, Dowling G, Zind R, White K, Johnson Griffin J, et al. Behavioral management of persistent auditory hallucinations in schizophrenia: outcomes from a 10-week course. *Journal of the American Psychiatric Nurses Association* 2002;**8**(3):84–91.

Ukoumunne 1999
Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organisation-based intervention in health and health care: a systematic review. *Health Technology Assessment* 1999;**3**(5): iii–92.

Wittek 2016
Wittek CT, Finserås TR, Pallesen S, Mentzoni RA, Hanss D, Griffiths MD, et al. Prevalence and predictors of video game addiction: a study based on a national representative sample of gamers. *International Journal of Mental Health and Addiction* 2016;**14**(5):672–86.

Xia 2009
Xia J, Adams CE, Bhagat N, Bhagat V, Bhoopathi P, El-Sayeh H, et al. Loss to outcomes stakeholder survey: the LOSS study. *Psychiatric Bulletin (London, England)* 2009; **33**(7):254–7.

Yang 2015
Yang CY, Lee TH, Lo SC, Beckstead JW. The effects of auditory hallucination symptom management programme for people with schizophrenia: a quasi-experimental design. *Journal of Advanced Nursing* 2015;**71**(12):2886–97. [PUBMED: 26283291]

* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

JL: development and writing of protocol.

MV: development and writing of protocol.

GH: development and writing of protocol.

DECLARATIONS OF INTEREST

JL: none known.

MV: has an interest in the topic of gaming for people with schizophrenia. The Academy of Finland and Turku University Hospital has also offered a grant to conduct a series of systematic reviews related to people with serious mental disorders.

GH: none known.

SOURCES OF SUPPORT

Internal sources

- Royal Derby Hospital Medical School, UK.

Lead author Jack Lloyd is a student at this university.

- School of Nursing, The Hong Kong Polytechnic University, China.

Employs review authors Grace Ho and Maritta Välimäki.

- Department of Nursing Science, University of Turku, Finland.

Employs review author Maritta Välimäki.

- Turku University Hospital, University of Turku, Finland.

Employs review author Maritta Välimäki.

External sources

- No sources of support supplied