Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"Do people who participate in clinical trials / research have better health outcomes (mortality / reduced symptoms / reduced recovery time) than people who do not?"

Clarification of question using PICO structure

Patients:	Health care patients / service users
Intervention:	Participation in clinical trials / research
Comparator:	Non participation in clinical trials / research
Outcome:	Improved health outcomes

Clinical and research implications

One well-conducted systematic review suggested that when participants are invited to participate in a randomised controlled trial, in addition to being informed about the risks and harms of specific clinical interventions, they can also be told that participating in a trial is likely to result in similar outcomes as if they receive similar treatment outside the trial. Similarly, other authors stated that patients being considered for entry into trials can be reassured that they will not be disadvantaged by entering a trial.

In contrast, some authors stated that more patients should be encouraged to enroll in clinical trials due to an apparent improvement in some outcomes. However, authors also noted that disclosure of this information to potential clinical trial participants may represent an ethical conflict and should be carefully considered in light of existing ethical guidelines.

Research implications were not often reported in the included studies. Authors reported that randomised comparisons with adequate sample sizes are needed to provide reliable evidence of potential differences in outcomes between patients who participate in randomised trials compared with those who do not participate. Some authors suggested that their studies required further validation at other institutions, preferably on a multi-institutional basis, because the situation may be different at other institutions.

What does the evidence say?

Number of included studies/reviews (number of participants)
We identified one systematic review (SR) (five randomised controlled trials (RCT) and 80 cohort studies with a total of 143,845 patients were included) (Vist et al. 2009) and six non-randomised studies (n=5,948 participants) that met the inclusion criteria.

Main Findings
The systematic review (Vist et al. 2009) evaluated 136 comparisons and found that in the majority of these comparisons, there were no statistically significant differences in outcomes between participants who were in included in a RCT compared with participants outside a RCT; eleven comparisons reported better outcomes *within* RCTs, and ten found better outcomes *outside* RCTs. With regards to mortality, 34 of the 37 comparisons (21 studies) reported no statistically significant differences. Only three studies reported a statistically significant lower risk of dying for patients treated within RCTs.

The non-randomised studies evaluated various groups of patients including those who had surgery for gastro-oesophageal reflux (Engström et al. 2012), inpatients with acute schizophrenia (Halbreich et al. 2008), patients with advanced non-small cell lung cancer (Rajappa et al. 2008; Tanai et al. 2009), women with ovarian cancer (Robinson et al. 2009), and patients with advanced gastric cancer (Tanai et al. 2011). The results from these studies varied. Three of the studies reported no differences in outcomes, or no clinically significant differences, between patients who were enrolled in a trial compared with patients who were not enrolled in a trial (Engström et al. 2012; Tanai et al. 2009; 2011).

In contrast, three other studies reported that patients who enrolled in clinical trials had better outcomes than patients in who did not participate in a trial. For example, Halbreich et al. (2008) reported that patients in a trial had a shorter length of hospital stay (6.75 days vs. 15.3 days), less physical restraints (0% vs. 21.9%), and less use of antipsychotics as chemical restraints (0% vs. 19.8%) compared to other psychiatric patients not enrolled in a trial. The study by Rajappa et al. (2008) reported that median overall survival was significantly longer (9.5 months vs. 7 months, P=0.005), and the percentage of patients surviving at one-year were significantly higher (42.5% vs. 25%, P=0.02) in patients who participated in a trial compared to patients outside of a clinical trial. Differences in response rate (RR) and progression free survival (PFS) were, however, not significantly different. Similarly, the study by Robinson et al. (2009) reported that overall survival for women with ovarian cancer was significantly longer for women who participated in a clinical trial compared with those who did not (median 46 vs. 24 months, P=0.03). Progression free survival was not significantly different between groups (P=0.08), although it favoured patients in a clinical trial (median 23 vs. 9 months).

Authors Conclusions

There was no general consensus amongst the study authors. Based on a systematic review of the evidence, Vist et al. (2009) concluded that participation in RCTs was associated with similar outcomes to receiving the same treatment outside RCTs. The study by Engström et al. (2012) concluded that participation in a RCT did not influence outcomes. Two studies conducted in different cancer patients by Tanai (2009; 2011) both concluded that there was no evidence to suggest that there was any difference in characteristics and clinical outcomes between trial participants and non-participants.

Three other non-RCTs made very different conclusions. The authors of Halbreich et al. (2008) concluded that patients who participate in structured clinical research had better outcomes than patients in the same non-research hospital wards. Rajappa et al. (2008) and Robinson et al. (2009) both concluded that cancer patients enrolled on clinical trials had better overall survivals compared with those not enrolled on a clinical trial.

Reliability of conclusions/Strength of evidence

The systematic review was methodologically well reported, and the conclusions are likely to be reliable. Most of the non-RCTs were well-conducted, but these types of studies (e.g. prospective and retrospective cohorts) are prone to bias.

What do guidelines say?

Not applicable

Date question received: 26/04/2012
Date searches conducted:
Date answer completed: 21/05/2012

References

Systematic Reviews

1. Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: MR000009. DOI: 10.1002/14651858.MR000009.pub4.

Primary Studies

2. Engstrom C, Jamison G, Devitt P, Irvine T, Watson D. Impact of Participation in Randomized trials on outcome following surgery for gastro-oesophageal reflux. *January 2012 Wiley online Library. DOI 10.1002/bjs.8666#*
3. Halbreich U, Smail N, Tu X, Halbreich J. Participation in Clinical Trials May Improve Care of Acute Schizophrenia Inpatients in a General Hospital. *CNS Spectrum, 13, 2008, 757-61.*
4. Rajappa S, Gundeti S, Uppalapati S, Jiwatani S, Abhyankar A, Pal C, Digumarti R. Is there a positive effect of participation on a clinical trial for patients with advanced nonsmall cell lung cancer? *Indian Journal of Cancer. October–December 2008. Volume 45. Issue 4*
5. Robinson W, Ritter J, Rogers A, Tedjarati S, Lieberenz C. Clinical Trial Participation is Associated with Improved Outcome in Women with Ovarian Cancer. *Int J Gynecological Cancer 2009;19: 124-128*
6. Tanai C, Nokihara H, Yamamoto N, Kunitoh H, Yamamoto N, Sekine I, Ohe Y , Tamura T Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials. British Journal of Cancer (2009) 100, 1037–1042. doi:10.1038/sj.bjc.6604982
7. *Tanai C, Nakajima T, Nagashima K, Kato K T Hamaguchi, Yamada Y, Muro K, Shirao K, Kunitoh H, Matsumura Y, Yamamoto S, Shimada Y,* Characteristics and Outcomes of Patients With Advanced Gastric Cancer Who Declined to Participate in a Randomized Clinical Chemotherapy Trial. *Journal of Oncology Practice VOL. 7, ISSUE 3*

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
1. Vist (2009)	March 2007	This systematic review compares participants of randomised controlled trials with non-participants of randomised controlled trials. Analysis were only included that compared patients that received the same clinical intervention in both the case of participation and non-participation. Outcomes of interest were mortality, morbidity, and clinically important changes in outcomes measured on a continuous scale. Cohort studies and randomised controlled trials that made suitable comparisons were included.	5 randomised controlled trials & 80 cohort studies were included in this review with a total of 143,845 patients. (86,640 in RCTS and 57,205 treated outside of RCTS)	None of the 5 RCTs found statistically significant differences in outcomes (i.e. side effects, patient satisfaction, pain reduction, change in 6 min walk distance) between patients treated within and outside RCTs. **Dichotomous outcomes:** Of the 80 cohort studies that compared partipants randomised to a RCT vs. participants not randomised to a RCT, no statistical significant differences were found for 85 of the 98 comparisons. Eight comparisons reported statistically significant **better** outcomes for patients treated within RCTs: One partially controlled adjusted comparison found that lung cancer patients in an RCT had a lower risk of dying inside RCT (RR 0.39, 95% CI 0.18 to 0.83) (Davis 1985). One poorly controlled comparison that adjusted for treatment (total parenteral nutrition or not) found that malnourished surgical patients in the RCT had a lower risk of complications (RR 0.60, 95% CI 0.42 to 0.86) (Williford 1993). One study found better blood pressure control inside the RCT (RR 0.73, 95% CI 0.56 to 0.97) (Martinez-Amenos1990a), a lower 18 year mortality after a health check without further intervention (RR 0.59, 95% CI 0.45 to 0.78) (Strandberg 1995) and a lower 30	Low

				day mortality after surgery in high risk patients (RR 0.23, 95%CI 0.07 to 0.77) (Rigg 2000a). One study found lower relapse rates for lymphocytic leukaemia in children receiving maintenance chemotherapy (RR 0.27, 95% CI 0.07 to 0.99) (Baum 1979), and more successful pregnancies after oocyte retrieval with different anaesthetics (RR 0.81, 95% CI 0.70 to 0.93 and RR 0.84, CI 0.75 to 0.95) (Rosen 1987a; Rosen 1987b). Five comparisons reported statistically significant **worse** outcomes for patients treated within RCTs: One found a higher risk of breast cancer recurrence among women who had received mastectomies within an RCT compared with women similarly treated outside the RCT (RR 2.79, 95%CI 1.04 to 7.53) (Blichert-Toft 1988b). One found that medical abortion was more acceptable to women in a preference trial than in the RCT (RR 5.36, 95% CI 1.66 to 17.28) (Henshaw 1993a). One found better satisfaction with the use of nasal tube for endoscopy outside of RCT than inside (RR 1.51, 95%CI 1.22 to 1.87) (Mori 2006b), one found greater rate of success for treating plantar fasciitis (foot disorder) with sham electrohydraulic high-energy shockwave treatment outside of the RCT than inside the RCT (RR 1.86, 95% CI 1.19 to 2.92) (Ogden 2004). One reported significantly higher satisfaction among women with medical abortion outside of an RCT than women who received medical abortion inside an RCT (RR 1.77, 95% CI 1.12 to 2.80) (Rørbye 2005a).	

				Continuous outcomes: No statistically significant differences in continuous outcomes were found for 30 of the 38 comparisons. Three comparisons reported statistically significant **better** outcomes for patients treated within RCTs: One study with two comparisons found that both couples who received pre-IVF counselling and couples who did not receive additional counselling pre-IVF in the RCT had lower anxiety than similar couples given or not given pre-IVF counselling outside of the RCT (SMD -0.37, 95% CI -0.72 to -0.01) (Emery 2003a), (SMD -0.80, 95% CI -1.26 to -0.34) (Emery 2003b). In one study of endoscopy patients who were given sedation inside RCT, they scored less troublesomeness than the patients who were sedated outside of the RCT (SMD -0.85, 95% CI -1.59 to -0.10) (Melchart 2002a) Five comparisons reported statistically significant **worse** outcomes for patients treated within RCTs: In one study the patients found the procedure more troublesome when given a placebo during endoscopy inside the RCT compared with similar patients given nothing during endoscopy outside the RCT (SMD0.47, 95%CI 0.14 to 0.80) (Abraham 2004b). In one study of young girls who were given growth hormone, they grew more outside the RCT than those who were treated inside the RCT (SMD 1.01, 95% CI 0.05 to 1.97) (McCaughey 1998). In three large, poorly controlled unadjusted studies looking at the effect of acupuncture for osteoarthritis of the	

				knee or hip, or chronic low back pain, or chronic neck pain patients reported less pain, higher reduction in pain and lower WOMAC score when treated with acupuncture outside RCT than similar patients treated with acupuncture in RCT (osteoarthritis patients, SMD0.40, 95%CI 0.28 to 0.52) (Witt 2006a) (chronic low back pain, SMD 0.10, 95% CI 0.04 to 0.15) (Witt 2006b) (chronic neck pain, SMD 0.07, 95% CI 0.02 to 0.13) (Witt 2006c). **Mortality (sub-group analysis)**: In 34 of the 37 comparisons (21 studies), no statistically significant differences in outcomes were found. One adjusted mortality comparison found a statistically significant lower risk of dying for patients treated within RCTs (Davis 1985). Two unadjusted mortality comparisons found a statistically significant lower risk of dying for patients treated within RCTs (Rigg 2000a; Strandberg 1995).	

Primary Studies (* Only primary studies with a publication date after March 2007 were included in this summary)

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
2. Engstrom (2012)	Patients were included in this analysis if they had surgery for reflux between 1994 and 2009. The analysis compared outcomes of patients who underwent the surgery as part of a randomised controlled trial with those who had the surgery outside of a trial. The discussed outcomes were the prevalence of	417 as part of randomised controlled trials, and 981 who underwent surgery	There were no significant differences in the analogue scores for dysphagia or satisfaction at one year, but the score for heartburn was significantly lower in the trial group (p<0.001), and more patients reported symptoms of abdominal bloating in the non-trial group (56.7% vs, 50.3%, P=0.046). At 5 years, dysphagia score for liquids was higher in the trial group (P=0.02). Both groups reported similar satisfaction	Study design has inherent risk of bias

	associated symptoms.	outside of a trial	scores; there were no differences in heartburn, bloating symptoms or rates of reoperative antireflux surgery.	
3. Halbreich (2008)	Patients were newly admitted patients with a diagnosis of schizophrenia who were severely agitated. The study compared outcomes for participants who took part in the trial with the general population of inpatients in the same county hospital. Outcomes reported were length of stay, the use of restraints and recidivism.	3,643 participants (32 patients on a clinical trial and 3,611 non-research inpatients)	Patients who were in the clinical trial had a shorter length of stay compared to the total psychiatric patients at the hospital during the study period (6.75 days vs. 15.3 days), less physical restraints (0% vs. 21.9%), and less use of antipsychotics as chemical restraints (0% vs. 19.8%).	Poorly reported - Study design has inherent risk of bias
4. Rajappa (2008)	Data was taken from the records of patients with untreated stage IIIb and IV non small cell lung cancer. A retrospective analysis of outcomes for those who took part in clinical trials was compared with people who did not take part in clinical trials. Outcomes studied were response rates, progression free survival and overall survival.	194 patients (54 on a clinical trial and 140 outside of it)	The differences in RR and PFS of patients who were treated inside and outside of a clinical trial were not significant (*P*=0.6164 and 0.0881 respectively). The differences in median OS (9.5 months vs. 7 months) and one-year survivals (42.5% vs. 25%) between the groups were significant (*P*=0.0052 and 0.022 respectively). However, the difference in the two-year survivals (14.8% vs 7.8%) was not significant (*P*=0.17). The difference in the median OS between the groups continued to be significant even after patients who received II line chemotherapy were censored (*P*=0.0437).	Study design has inherent risk of bias
5. Robinson (2009)	A retrospective analysis of data from a single clinic was used to identify patients treated for epithelial ovarian cancer between 2002 and 2007. The study identified 158 suitable patients. 53 had participated in clinical trials, 105 had not. Progression free survival and overall survival rates were used as outcome measures.	158 patients (53 participants and 105 non participants)	Overall survival was significantly longer for patients who participated in a clinical trial compared to non-participants (median 46 vs. 24 months, P=0.03). Progression free survival was not significantly different between groups (P=0.08), although it favoured patients in a clinical trial (median 23 vs. 9 months).	Study design has inherent risk of bias
6. Tanai	This study was a retrospective analysis	269 patients	Important differences were not observed in the clinical	Study design

(2009)	of data concerning patient characteristics and treatment outcomes for participants and non-participants in two randomised controlled trials for chemotherapy-naïve advanced non small-cell lung cancer. In this study, those who met the eligibility criteria but declined to participate in randomised trials, and chose to receive standard therapy were the 'non-participants'. The primary outcome was survival.	(196 participants and 73 non participants)	outcomes between participants and non-participants, for whom the response rates were 30.6 vs 34.2% (P=0.33) and the median survival times were 489 vs 461 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 0.965 (95% confidence interval: 0.73–1.28).	has inherent risk of bias
7. Tanai (2011)	This study was a retrospective analysis of data concerning patient characteristics and treatment outcomes for participants and non-participants in two randomised controlled trials for naïve advanced gastric cancer. Outcomes were discussed in terms of survival.	286 patients (190 clinical trials participants, and 96 non participants)	No significant differences were observed in the clinical outcomes between the participants and nonparticipants, for whom the median survival times were 367 vs. 347 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 1.21 (95% CI, 0.91 to 1.60). The response rate was 30.5% for the participants and 21.9% for the nonparticipants (*P*=0.121).	Study design has inherent risk of bias

Risk of Bias:

SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Vist et al. 2009	☺	☺	☺	☺	?

Non-RCTs

Study	RISK OF BIAS					
	Aims and objectives clearly stated?	Sufficient description of the groups and the distribution of prognostic factors?	Were groups comparable on all important confounding factors?	Was outcome assessment blind to exposure status?	Follow-up long enough for outcomes to occur?	Was an adequate proportion of the cohort followed-up?
Engstrom et al. 2012	☺	☺	☺	?	☺	☺
Halbreich et al. 2008	☺	☹	?	?	NA	NA
Rajappa et al. 2008	☺	☺	☺	?	☺	☺
Robinson et al. 2009	☺	☺	☺	?	☺	☺
Tanai et al. 2009	☺	☺	☺	?	☺	☺
Tanai et al. 2011	☺	☺	☺	?	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
DARE	1 research 19444 2 MeSH DESCRIPTOR Biomedical Research EXPLODE ALL TREES 26 3 MeSH DESCRIPTOR Clinical Nursing Research EXPLODE ALL TREES 31 4 MeSH DESCRIPTOR Community-Based Participatory Research EXPLODE ALL TREES 4 5 MeSH DESCRIPTOR Empirical Research EXPLODE ALL TREES 55 6 MeSH DESCRIPTOR Health Services Research EXPLODE ALL TREES 465 7 MeSH DESCRIPTOR Nursing Administration Research EXPLODE ALL TREES 10 8 MeSH DESCRIPTOR Peer Review, Research EXPLODE ALL TREES 3 9 MeSH DESCRIPTOR Qualitative Research EXPLODE ALL TREES 37 10 MeSH DESCRIPTOR Research EXPLODE ALL TREES 951 11 MeSH DESCRIPTOR Research Design EXPLODE ALL TREES 1979 12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 20116 13 MeSH DESCRIPTOR Trust EXPLODE ALL TREES 1 14 mental health trust* 6 15 trust* 448 16 mental health service* 313 17 MeSH DESCRIPTOR Community Mental Health Services EXPLODE ALL TREES 102 18 MeSH DESCRIPTOR Mental Health Services EXPLODE ALL TREES 557 19 clinic* 24249 20 MeSH DESCRIPTOR Outpatient Clinics, Hospital EXPLODE ALL TREES 71 21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 24573 22 #12 AND #21 13773	331	1

	23 reseach adj 2 active 0 24 research active 1 25 research act* 20 26 research adj2 act* 46 27 research adj2 intensive 5 28 #25 OR #26 OR #27 51 29 #21 AND #28 31 30 (research):TI 499 31 (trust*):TI 3 32 (service*):TI 517 33 #31 OR #32 520 34 #30 AND #33 18 35 (nhs):TI 32 36 #30 AND #35 1 37 nhs 13158 38 #22 AND #37 3928 39 mental 1921 40 #38 AND #39 331 Delete		
Primary studies			
CENTRAL	#1 "Clinical trial":ti,ab,kw 59320 edit delete #2 participation 7485 edit delete #3 outcomes 159917 edit delete #4 "research intensive" 10 edit delete #5 (#1 OR #4) 59330 edit delete #6 (#2 AND #3 AND #5) 371 Clinical trials 300	300	7
PsycINFO	8. PsycINFO; "clinical trial*".ti,ab; 15709 results. 9. PsycINFO; participation.ti,ab; 52560 results. 10. PsycINFO; outcomes.ti,ab; 111169 results. 11. PsycINFO; 8 AND 9 AND 10; 96 results.	96	
MEDLINE	1. MEDLINE; "clinical trial*".ti,ab; 176364 results.	358	

	2. MEDLINE; participation.ti,ab; 79593 results. 3. MEDLINE; outcomes.ti,ab; 298306 results. 4. MEDLINE; 1 AND 2 AND 3; 357 results. 5. MEDLINE; "research intensive".af; 124 results. 6. MEDLINE; 1 OR 5; 176484 results. 7. MEDLINE; 2 AND 3 AND 6; 358 results.		
EMBASE	2. EMBASE; participation.ti,ab; 92421 results. 3. EMBASE; outcomes.ti,ab; 388855 results. 5. EMBASE; "research intensive".ti,ab; 144 results. 6. EMBASE; "clinical trial*".ti,ab; 225391 results. 7. EMBASE; 5 OR 6; 225533 results. 8. EMBASE; 2 AND 3 AND 7; 502 results	502	
Methods studies From Cochrane	#1 "Clinical trial":ti,ab,kw 59320 edit delete #2 participation 7485 edit delete #3 outcomes 159917 edit delete #4 "research intensive" 10 edit delete #5 (#1 OR #4) 59330 edit delete #6 (#2 AND #3 AND #5) 371 edit delete Methods Studies 41	41	
Summary	**NA**	**NA**	

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