

Evidence-based fertility treatment: what do we mean?

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This article explores the meaning of ‘evidence-based fertility treatment’ and reviews the relevance of evidence-based health care to the proposed National Service Framework (NSF) for Infertility Services. It summarizes the principles of systematic literature reviewing and proposes an agenda for those developing the NSF. This agenda is illustrated by data from a preliminary review by the authors. The main strength of the proposed NSF lies in the National Evidence-Based Clinical Guidelines but the main weakness lies in the lack of rigorous positive evidence underpinning these guidelines. The NSF team will have to appraise, enhance, extend and synthesize these reviews. The lack of an NSF would threaten the future effectiveness and cost-effectiveness of infertility services in the UK.

The present article explores the meaning of ‘evidence-based fertility treatment’ in four sections. The first section reviews the recent development of ‘evidence-based health care’ and its relevance to the proposed National Service Framework (NSF) for Infertility Services. The second section summarizes the principles of systematic literature reviewing – the foundation stone of an evidence-based NSF. The third section proposes an agenda for those developing the NSF. The fourth section illustrates this agenda by reporting a preliminary review by the authors.

Evidence-based health care

Evidence-based health care stems from parallel developments on each side of the Atlantic in the second half of the twentieth century. The UK took the lead in establishing research and development (R and D) as a key activity within national health care systems (Department of Health, 1991). The resulting commitment to generate rigorous evidence about the effectiveness and cost-effectiveness of interventions in health care owed much to the earlier development of the randomized controlled trial (RCT), also led from the UK. There are examples of RCTs in the eighteenth century, notably to evaluate the treatment of scurvy (Pocock, 1983). The modern RCT has contributed increasingly to the evaluation of drugs, beginning with streptomycin (Medical Research Council, 1948). Twenty years later, Cochrane (1972) advocated applying RCTs to a much wider range of interventions.

Over the past 10 years Cochrane’s vision of using the resulting evidence to guide health care policy has given rise to both the worldwide Cochrane Collaboration (Chalmers *et al.*, 1997) and the R and D information strategy of the British National Health Service (NHS) (Sheldon and Chalmers, 1994).

Developments across the Atlantic, notably at the distinctive medical school of McMaster University in Ontario, focused on the use of evidence in the care of individual patients through the application of clinical epidemiology (Sackett *et al.*, 1991). These two developments converged in 1995 when David Sackett came to Oxford to found the Centre for Evidence-Based Medicine (CEBM) in close association with the NHS R and D Programme. Sackett *et al.* (1996) defined ‘evidence-based medicine’ (EBM) as:

‘the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research.’

Elaborating on this definition, the CEBM proposed four basic principles of EBM:

- clinical and other health care decisions should be based on best evidence from patients and populations
- the nature and source of the evidence to be used should depend on the problem to be solved rather than habit or tradition
- to appraise this evidence needs the integration of epidemiological skills with those of clinical expertise and pathophysiology
- this process is worthwhile only if translated into actions that affect patients

To give effect to these principles, Sackett *et al.* (1997) identified six key tasks of EBM:

- identify information needs – notably about diagnosis, prognosis and therapy
- convert these needs into answerable questions
- seek the best evidence to answer these questions – from clinical examination, diagnostic laboratory and research evidence
- appraise this evidence critically for its validity (that is, its closeness to the truth) and usefulness (clinical applicability)
- apply the results of this appraisal in clinical practice
- monitor one’s performance of these tasks

Characterized thus, EBM provides a rational scientific basis for clinical practice and medical education in the twenty-first century (for example, Campion and Russell, 2002). It identifies skills that clinicians can learn, practise and teach. Many health professionals have responded with enthusiasm to the opportunities provided by this new paradigm and, perhaps most importantly, there is evidence that it has been effective in changing practice (Sackett *et al.*, 2000).

Nevertheless, EBM has weaknesses. Sackett *et al.* (2000) often prefer clinical evidence to the values of patients and the costs to

Table 1. The essential phases of a systematic literature review

Number	Phase
0	Identifying the need for the review
1	Specifying the objectives of the review
2	Developing the review protocol
3	Searching the literature and retrieving the studies
4	Assessing studies for relevance
5	Assessing and grading studies for validity
6	Extracting data from the selected studies
7	Synthesizing data from the selected studies
8	Planning, writing, reviewing and finalising the report
9	Disseminating and implementing the report

Source: NHS Centre for Reviews and Dissemination, 2001.

the NHS. They often invoke individual studies rather than systematic literature reviews. In synthesizing evidence, they prefer clinical judgement to formal techniques like decision analysis. In focusing on individual clinical practice, they play down the issue of resource allocation within the NHS. However, in their defence, their textbook on EBM for clinicians has a natural complement in Gray's (2001) textbook on evidence-based health care (EBHC), written for 'those who make decisions about groups of patients'.

However, the proposed NSF will guide both clinical practice and NHS resource allocation, and therefore needs a philosophy that emphasizes common principles while recognizing the different perspectives of those who commission and provide fertility services. Cochrane (1972) provides a useful text, which we have paraphrased to highlight its relevance to the NSF:

The development of effective and efficient fertility treatment needs hard evidence, preferably from randomized trials that the use of each procedure either alters the natural history of infertility or otherwise benefits many patients at a reasonable cost.

(Paraphrased from Cochrane, 1972)

Thus Cochrane was proposing three criteria, familiar today, for evidence-based health care:

- effectiveness – does the procedure generate health gain in clinical practice?
- acceptability – is the procedure acceptable to patients, their partners and staff?
- efficiency – does the procedure give 'good value for money'?

Systematic reviews

Systematic reviews are 'overviews of scientific studies that use explicit, systematic and therefore reproducible methods to locate, select, appraise and synthesise relevant and reliable evidence' (Greenhalgh, 1997). Meta-analyses are 'statistical syntheses of the results of similar but separate studies' (Chalmers, 2001). Mulrow (1995) summarized the case for systematic review and meta-analysis thus:

'Systematic reviews of research evidence establish whether scientific findings can be generalised across populations, settings and treatment variations; or whether they vary significantly. Explicit methods used in systematic reviews limit bias and improve the validity and reliability of conclusions. Meta-analysis increases the precision of estimates of treatment effects.'

Like all other scientific fields, systematic reviewing does not have a single methodological approach that can be applied in all circumstances. When the treatment or procedure of interest is well defined, consistent between settings, and amenable to evaluation by randomized controlled trials (for example, drug therapy for infertility), the designs of the studies to be included in systematic reviews can be defined *a priori*; for example, they can be limited to well-conducted randomized trials. Systematic reviews in fields in which these conditions apply fall within the scope of the worldwide Cochrane Collaboration, the very rigorous criteria of which Clarke and Oxman (2002) have delineated.

In contrast, when the treatment or procedure of interest is less easy to define, likely to vary between settings, and more difficult to evaluate by RCTs (for example, counselling for infertility), there is more scope for judgement in the choice of review methods and the selection of studies. Nevertheless, the requirement for methods to be explicit and reproducible cannot be relaxed. Indeed, this principle is evident throughout the guidance published by the NHS Centre for Reviews and Dissemination (NHS CRD, 2001). Given the close working relationship between the UK Cochrane Centre and the NHS CRD (Sheldon and Chalmers, 1994), these two approaches may be regarded as two points on the spectrum of rigorous approaches to the science of systematic reviewing. The ten essential phases of a systematic review, equally applicable whether the review is for the Cochrane Collaboration or the NHS CRD, are shown (Table 1).

Towards an NSF for Infertility Services – setting the agenda

What are the implications of this ten-phase agenda for the proposed NSF? There have been two previous attempts to review evidence across this field. First, Russell *et al.* (1998) contributed to the 35th Royal College of Obstetricians and Gynaecologists (RCOG) Study Group (Templeton *et al.*, 1998) by offering general advice for reviews on fertility treatment. We reported a systematic review of systematic reviews in this field, limited to those listed by the end of 1997, in the *Cochrane Database of Systematic Reviews (CDSR)*, the *Database of Reviews of Effectiveness (DARE)* or *Medline*, and those added by members of the 35th Study Group. This review yielded 100 studies, of which 23 were not relevant and a further 37, though relevant, were not valid systematic reviews. *CDSR* contributed 16, *DARE* eight, *Medline* 11 and the 35th Study Group five of the 40 relevant systematic reviews (Russell *et al.*, 1998).

The quality of these 40 reviews was assessed by deriving seven three-point items from seven of the phases listed above, namely 1 and 3 through 8. For each review, we summed the seven resulting scores: two if it provided evidence that it had completely fulfilled that item; one if it provided partial evidence; and zero if it failed or did not mention that item. As our team did not include an obstetrician, we were effectively scoring

Table 2. National Evidence-Based Clinical Guidelines on the management of infertility

Strength of recommendation	A (at least one randomized controlled trial)	B (other studies)	C (expert opinion)	Total
Initial investigation and management (RCOG, 1999a)	3 ^a	9	19	31
Management in secondary care (RCOG, 1999b)	20 ^b (9 negative)	17	26	63
Management in tertiary care (RCOG, 2000)	12 ^c (6 negative)	20	25	57
Total	35 (15 negative)	46	70	151

^aIn brief, the three positive Grade A recommendations were:

- general practitioners (GPs) should follow local management protocols
- GPs should advise women presenting with infertility to take folic acid supplements
- GPs should advise obese women seeking to conceive to lose weight under supervision

^bIn brief, the 11 positive Grade A recommendations were:

- bromocriptine is effective in men with hyperprolactinaemia
- intrauterine insemination is effective for men with seminal abnormalities
- treatment of varicoceles is effective in oligospermic men
- clomiphene is effective for anovulation in selected women
- (i) gonadotrophin therapy and (ii) laparoscopic ovarian drilling are effective for anovulation in women with clomiphene-resistant polycystic ovarian syndrome
- dopamine agonists are effective for anovulation due to hyperprolactinaemia
- (i) surgical ablation and (ii) ovarian stimulation are effective in subfertile women with endometriosis
- (i) ovarian stimulation with intrauterine insemination and (ii) gamete intrafallopian transfer are effective for couples with unexplained infertility

^cIn brief, the six positive Grade A recommendations were:

- adjuvant gonadotrophin-releasing hormone is effective in IVF
- urinary-derived gonadotrophin is more effective than human menopausal gonadotrophin
- recombinant follicle stimulating hormone is more effective than urinary-derived gonadotrophin
- placing embryos in the mid-cavity of the uterus is most effective
- luteal phase support is effective in IVF with gonadotrophin-releasing hormone agonists
- when expected success for intracervical donor insemination is less than 6%, use intrauterine

whether the review included appropriate statements without questioning their clinical validity. Although the 16 CDSR reviews averaged 11.5 points out of the total of 14, the other 24 reviews averaged only 9.1. We attributed this substantial difference to quality assurance within the Cochrane Collaboration. Therefore, we made four recommendations for improving reviews outside the Cochrane Collaboration, addressed to reviewers, research funders, journals and universities. In particular, we urged reviewers to adopt recognized standards, either by registering their reviews with the Cochrane Collaboration or by espousing the criteria set by the NHS CRD (Russell *et al.*, 1998).

Soon after this review, the RCOG (1999a, 1999b, 2000) started work on *National Evidence-Based Clinical Guidelines for Management of Infertility* funded by the NHS Executive. Together, these guidelines made a total of 151 recommendations (Table 2). However, despite access to the 40 reviews identified by Russell *et al.* (1998), the guideline developers found little evidence that was both rigorous and relevant to their task (compare with Leese and Whittall, 2001). Indeed, only 35 of their recommendations used findings from RCTs. Even worse, 15 were negative findings such as 'there is no evidence that treating infection of the male genital tract will

improve fertility' (RCOG, 1999b). Therefore, the current national guidelines include only 20 recommendations that are both rigorous and positive (listed in Table 2). Nevertheless, these recommendations provide the best starting point for the proposed NSF.

Those responsible for the NSF will need to define how its scope should relate to that of the national guidelines. Given the shortage of good evidence in those guidelines, they should search thoroughly for systematic reviews using all recognized methods: searching all potentially relevant electronic databases; hand-searching key journals; consulting experts and the pharmaceutical industry; and scanning all reference lists thus identified. This task is illustrated in the next section which updates Russell *et al.* (1998).

Critical appraisal (NHS CRD, 2001) is likely to show that few existing reviews fulfil the needs of the NSF precisely. Some reviews will not be systematic in intent. Others will be poorly executed in practice. Some will be too narrow in scope, for example if restricted to RCTs. Other reviews will be too broad, for example if including studies inconsistent with NHS practice. To address these problems of internal and external validity, the NSF team will need to update some reviews and commission others *de novo* (Eccles *et al.*, 2001). In developing the NSF itself,

Table 3. Formulation and outcome of *Medline* search (1998–2002)

Step	Command	Number of papers found
1	META?1ANALYS*	5972
2	FERTILITY	7986
3	INFERTILITY	6692
4	#2 or #3	13 115 ^a
5	#1 and #4	63
6	LA = ENGLISH	1 915 135
7	#5 and #6	59
8	ANIMAL	576 152
9	#7 not #8	56

^a1563 studies used both 'fertility' and 'infertility' as keywords.

the NSF team should grade all recommendations and link them explicitly to the supporting evidence. Although the RCOG adopted this procedure in principle (Table 2), there is merit in using a stricter four-point classification for the strength of recommendations (Eccles *et al.*, 2001). Even recommendations derived from at least one RCT would not achieve grade A unless directly relevant to the NSF recommendation.

Finally, it is essential that the NSF identifies the main gaps in the resulting evidence base, and sets an R and D agenda for fertility treatment, say for the next decade. Leese and Whittall (2001) argued that, because the Human Fertilisation and Embryology Authority (HFEA) could not conduct clinical research, it had a responsibility to encourage such research to strengthen the available evidence. Unless the NSF team accepts the same responsibility, the evidence will remain weak.

Towards an NSF for Infertility Services – illustrative literature review

Specifying the objectives

Lack of time and obstetric expertise led us to limit our objectives to illustrating the reviewing process needed for the NSF by extending the systematic search by Russell *et al.* (1998) from the beginning of 1998 until the end of 2002.

Developing the protocol

In keeping with these limited resources and objectives we developed the limited protocol represented here.

Searching the literature

We limited our search to reviews listed in *CDSR*, *DARE* or *Medline* in December 2002 but not in December 1997, at least in the same form. The NSF team should add at least *Embase* to these databases.

We identified 52 essentially new reviews all key-worded as 'infertility' in *CDSR* and 18 more in *DARE* key-worded as 'infertility' or 'fertility'. Within *Medline* we sought all essentially new papers in English about humans whose abstracts

Table 4. Reasons for excluding studies

Subject of excluded studies	Number of studies
Not relevant (46)	
Contraception and family limitation	8
Treatment for other condition (no direct fertility outcomes)	7
Complications of fertility treatment	7
Endometriosis treatment (no direct fertility outcomes)	5
Treating complications of infertility	5
Pregnancy and birth	4
Prevention of sexually transmitted infections (no direct fertility outcomes)	3
Other disease (no treatment or direct fertility outcomes)	2
Hysterectomy	2
Health of fetus or infant	1
Psychology of, and attitudes to, fertility	1
Population study (human sex ratios)	1
Relevant but not valid (15)	
Comment on previous meta-analysis	5
Non-systematic review	5
Report of single study (randomized controlled trial)	1
Methodology of systematic reviews	1
Prior publication of material in an included <i>CDSR</i> review	1
Use of meta-analysis results for cost-effectiveness	1
Cochrane Review from 1997 listed in <i>Medline</i> as 1998	1
Total	61

CDSR: Cochrane Database of Systematic Reviews.

included '(in)fertility' and 'meta-analysis' (with minor spelling variations). This generated 56 reviews (Table 3). The NSF team should also consider studies whose abstracts include both 'review' and 'literature'. This will identify several systematic and many non-systematic reviews.

As 16 of the reviews identified through *CDSR* or *DARE* also appear in *Medline*, our search identified a total of 110 distinct studies.

Selecting relevant and valid studies

We assessed whether each study was 'relevant' in addressing the nature or causes of infertility, diagnostic tests or treatment for infertility, and this eliminated 46 studies (Table 4). We next assessed whether each remaining study was 'valid' in reporting a systematic review as defined at the beginning of this chapter, and this eliminated a further 15 studies (Table 4).

Table 5. Sources and numbers of relevant valid reviews

Subject of review	Source			Total
	CDSR (2002)	DARE (2002)	Medline (2002 but not CDSR or DARE)	
Nature and causes of infertility	0	1	6	7
Diagnostic tests for infertility	0	2	2	4
Treatment of male infertility	6 ^a	2 ^a	1	9 ^a
Treatment of female infertility	18 ^a	7 ^a	6	31 ^a
Total	23	11	15	49

^aTwo studies, one in *Cochrane Database of Systematic Reviews (CDSR)* and one in *Database of Reviews of Effectiveness (DARE)*, reviewed treatment for both men and women.

The remaining 49 valid systematic reviews apparently relevant to the proposed NSF are summarized (Table 5; see also Appendix A and Appendix B of Russell and Russell, 2003, the electronic report that reproduces and extends this paper, which list the 49 systematic reviews and the 61 excluded studies, respectively). In addition, almost all of the 40 valid systematic reviews identified by Russell *et al.* (1998) are in urgent need of updating, if indeed still relevant to the proposed NSF.

Grading studies

As reported above, our previous scale summed seven three-point items to yield a maximum score of 14 (Russell *et al.*, 1998). In doing so, our scale gave more credit to quality of reporting than to quality of reviewing. More recently, Moher *et al.* (1999) have published the Quality of Reports of Meta-analyses (QuORUM) statement, the 23 items of which focus on quality of reporting. This publication stimulated us to revise our scale to balance quality of reviewing and reporting. In doing so, we sought both to use an existing scale that was similar to our own and to be consistent with the ten-phase agenda of the NHS CRD (2001).

The scale validated by Oxman and Guyatt (1991) began with nine three-point items, each with three possible answers: 'yes', 'partially' or 'can't tell', and 'no'. Their score came from a final seven-point item 'How would you rate the scientific quality of this review?', summarizing all the previous items. The first eight items form four pairs, each corresponding to one of our seven previous items. Within each pair, one item asked about reporting and the other about reviewing, thus achieving the balance we sought. In updating our scale, we therefore adopted the basic structure of Oxman and Guyatt (1991) but extended it to cover most of the ten phases of the NHS CRD (2001) agenda. We also assessed scientific quality more widely than Oxman and Guyatt (1991), and summed all items to yield a single score with a maximum of 25 (Table 5).

Scores out of 25 for a stratified sample of six reviews published since 1998 (one each on male infertility and female infertility from each of three databases: CDSR, DARE and Medline) are shown (Table 6). Both CDSR reviews scored much more

than the other four reviews. Both DARE reviews had intermediate scores. One of the Medline reviews was mediocre and the other was poor. None of the four non-CDSR reviews reported using two reviewers. Only one searched more than one electronic database. Unfortunately, this pattern is consistent with that reported by Russell *et al.* (1998). Many reviewers are still not adopting recognized quality standards, set for example by the Cochrane Collaboration or NHS CRD.

Extracting the data

Given our lack of obstetric expertise, we tabulated the published abstracts of the six scored reviews under the basic headings adopted by the Cochrane Collaboration: objectives, search strategy, selection criteria, analysis, and results and conclusions (see Appendix C of Russell and Russell, 2003). If an abstract provided insufficient detail on these topics, we abstracted other sections of the paper, still keeping close to the original text. In this way, we again avoided the need for clinical interpretation.

Synthesizing the data

On account of our limited objectives and resources, we have not synthesized the 49 included reviews.

Writing and reviewing the report

This report of our illustrative review includes: a brief protocol (under the heading 'Towards an NSF for Infertility Services – illustrative literature review'); our search strategy (Table 3); a summary of studies excluded (Table 4) and included (Table 5); and a summary of six studies sampled and graded (Table 6). Russell and Russell (2003) includes appendices that list the included and excluded studies and tabulate the six graded studies. In effect, we used the referees of this Supplement to *Human Fertility* to review the resulting report.

Disseminating and implementing the report

In effect, we used the publishers and distributors of *Human Fertility* to disseminate this report.

Table 6. Breakdown of updated validity scores for relevant valid reviews

Question ^a [phase of review ^b]	CDSR1 (Blake, 2002)	CDSR2 (Evers, 2002)	DARE1 (Agrawal, 2000)	DARE2 (Zeyneloglu, 1998)	Medline1 (Honore, 1999)	Medline2 (Tournaye, 2002)
1. Specified objectives? [1] Scores: 2: precise; 1: vague; 0: none	2	2	1	2	1	1
3a. Search methods stated? [3] Scores: 2: yes; 1: partially; 0: no	2	2	2	1	2	2
3b. Search comprehensive? [3] Methods: electronic, hand-searching journals, reference lists, authors etc, industry Scores: 3: ≥ two electronic and ≥ two other; 2: ≥ three methods including ≥ one electronic; 1: three non-electronic methods or any two methods; 0: one or no methods	3	3	1	1	1	2
4a. Selection of reviews reported? [4 and 5] Components: criteria, table of included studies, table of excluded studies Scores: 2: all three; 1: two or one; 0: none	2	2	2	1	1	1
4b. Number of selecting reviewers? [4 and 5] Scores: 2: ≥ two; 1: one only; 0: selection implicit	2	2	1	1	0	0
5a. Validity criteria reported? [5] Scores: 1: yes; 0: no	1	1	0	1	0	0
5b. Validity assessed and used? [5, 7, 8] Scores: 2: yes; 1: partially; 0: no	1	2	1	2	1	1
6. Methods of synthesis reported? [6 and 7] Components: data extraction and analysis Scores: 2: both; 1: one; 0: neither	2	2	2	2	2	2
7. Synthesizing the data rigorously? [7] Methods: qualitative overview, meta-analysis, clinical and statistical homogeneity assessed and used Scores: 3: all three; 2: two 2; 1: one: 0: none	2	3	2	2	1	2
8. Conclusions valid? [8] Components: valid for health care and for research Scores: 2: yes; 1: partially; 0: no	2	2	1	2	0	2
9. Scientific quality of overview? [1 to 8] Scores: 4: minimal flaws; 3: minor flaws; 2: major flaws; 1: extensive flaws; 0: invalid	3	3	2	2	1	3
Total (out of 25)	22	24	15	16	10	16

^aBased on the methodological recommendations of Russell *et al.* (1998).^bDefined by NHS Centre for Reviews and Dissemination (2001) and listed in Table 1.

Conclusions

The main strength of the proposed National Service Framework for Infertility Services lies in the existence of the corresponding National Evidence-Based Clinical Guidelines. The main weakness lies in the lack of rigorous positive evidence underpinning

these guidelines, despite a plethora of published literature reviews. The NSF team will have major opportunities to appraise, enhance, extend and synthesize these reviews, and to set a research agenda to extend the limited evidence. We judge that the lack of an NSF would represent a threat to the future effectiveness and cost-effectiveness of infertility services in the UK.

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