

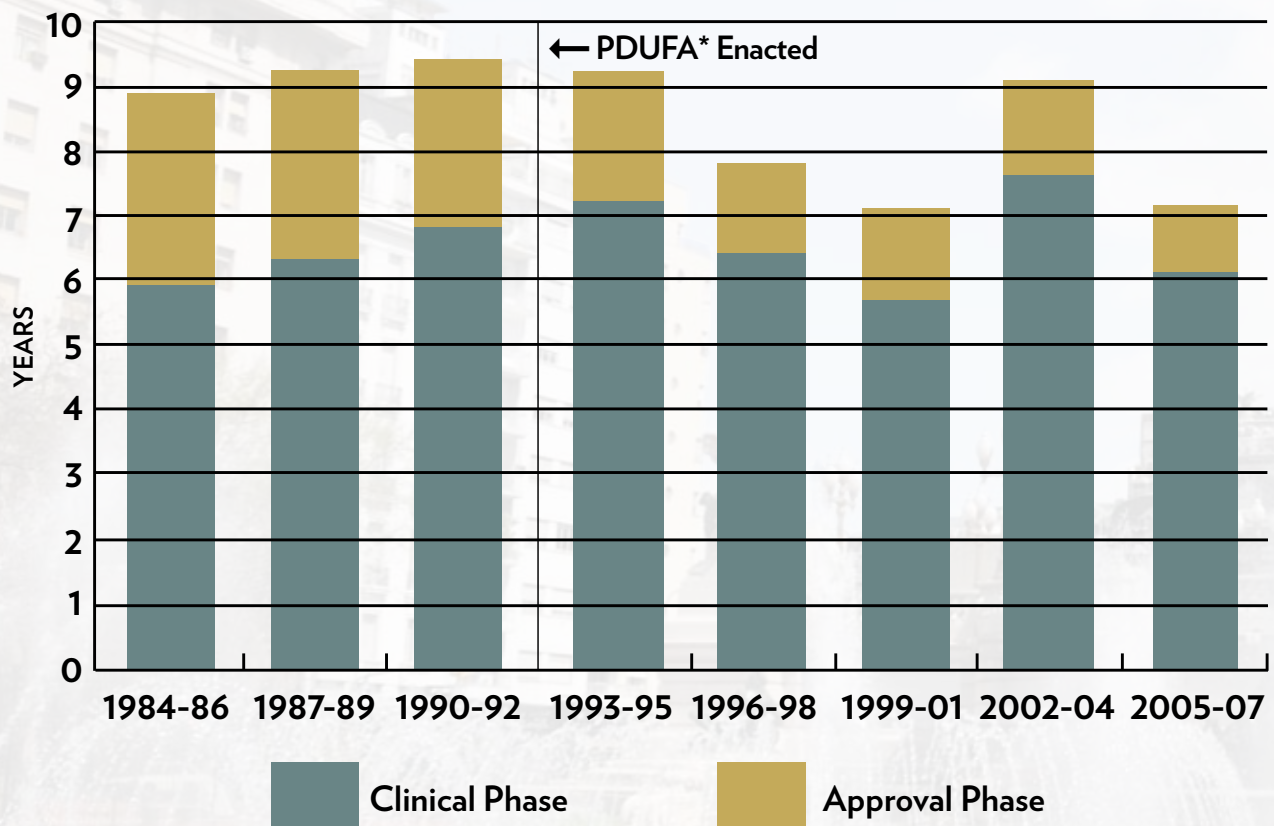
FOR PEOPLE WITH RARE DISORDERS

JUSTICE NOT DOGMA

I AM WRITING THIS A FEW DAYS AFTER participating in the Congress of the World Federation of Hemophilia (WFH) in Buenos Aires, Argentina. As always, seeing the bleeding disorders community come together with their treaters and the industry was a great experience, although mixed in some ways. It was great to observe how the availability of treatment products has emancipated these vulnerable patients. Mixed in with this good news, however, was the sobering realization of how much more needs to be done.

Which brings me to the story of Cheryl D'Ambrosio, whom I met at the Congress. Cheryl's story can be found on www.poolingblood.com, and I encourage you to learn about her journey caring for her two now-adult stepdaughters with coagulation factor V deficiency, a disorder of the clotting system affecting one in 1 million people. I was affected and inspired by Cheryl's story of her struggle for recognition and treatment of her girls' condition. People with Factor V deficiency need, like in all congenital bleeding disorders, replacement of the missing factor if they are not to suffer life-threatening bleeds. The disorder has been identified and understood in the medical community for a very long time, and the best form of treatment would be, as is the case with hemophilia, a concentrate of Factor V. There are no such products available, and Cheryl's girls,

FIGURE 1: Drug development and approval times



* Prescription Drug User Fee Act

like all of these patients, depend on the transfusion of plasma for treatments. Hearing Cheryl's tale of her struggle against ignorance and constant impediments to access for the treatment reminded me of the situation faced by individuals with hemophilia 40 years ago. Transfusion of plasma, with its large volume, its propensity to result in allergic reactions and its risk of pathogen transmission, is, clearly not the preferred therapy. All these undesirable properties would be avoided with the development of a concentrate. The isolation of Factor V from plasma is not too difficult—I myself have had occasion to do it



We salute Cheryl D'Ambrosio, a woman of style and courage.

in the distant days of when I was a coagulation researcher. Why has this simple chemistry not given rise to a product?

Some might speculate that the reason lies on the rarity of the condition. Research suggests that Factor V deficiency affects one in 1 million individuals. Yet there are inherited protein deficiencies, which are equally rare, where products exist. For example, concentrates

of fibrinogen for the treatment of hereditary fibrinogen deficiency have been approved by regulators, and hereditary fibrinogen deficiency is rarer than Factor V deficiency. This naturally causes us to ask, "What makes the development of drugs such a difficult and lengthy process?" Clearly, it is expensive to develop medicines, involving as it does much research and development. However, the longest—and therefore costliest—phase of drug development in the so-called clinical phase, during which the drug is tried out—or trialed—in patients to ensure that it is safe and that it works, or is efficacious. [Figure 1] Such "clinical trials"



are, effectively, experiments in people to ensure safety and efficacy in the drug before it is approved for general use in the patient population.

The science of clinical trials has evolved over the past 50 years, and it has reached its pinnacle in the so called “randomized clinical trial” or RCT. In an RCT, the target patient population is split into two groups, one of which receives the drug, another of which receives an inert agent—the placebo. This “random” allocation of the treatment ensures that any contributors to the observed affect are solely the result of the drug, and do not ensue from particular features of individual patients, doctors, etc.

Now, RCT’s are absolutely the best way of assessing a drug’s efficacy when the number of patients is large and when the mechanism of the drug’s action is relatively uncertain. Under these conditions, an RCT can be designed, which will allow an answer to be generated on the drug’s efficacy. Such an RCT will generally need a substantial number of patients, will take a long time to conduct, and will therefore cost a lot of money. Many of these limitations are not too problematic for mass-produced pharmaceutical drugs intended for large numbers of patients—think statins or anti-hypertensives (such as erectile dysfunction drugs).

For biological drugs used to treat rare disorders such as coagulation factor deficiencies, the use of RCTs is very

Figure 2: Parachutes— should their use be subject to randomized trials?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

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Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.⁶

Meta-analysis

Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger’s and Begg’s tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

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BMJ 2003;327:1459–61



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problematic. Indeed, when the disease is so clearly understood and associated with a specific protein deficiency, such as hemophilia, the use of RCT can be viewed as not only impractical but unethical. A famous article some years ago pointed out that the use of parachutes has never been validated through an RCT. (Figure 2). Prof. Wolfgang Schramm (see profile on page 24) has remarked that forcing hemophiliacs to undergo RCT's for clotting factors would be a similar situation. And yet, this is precisely what some extremist advocates of RCTs would have patients do. Despite the impossibility of generating statistical evidence of efficacy with the small patient numbers possibly into rare disorders, some advocates of evidence-based medicine, a principle that I passionately support, insist on RCTs for treatments for these patients. Recently, some of these people achieved media publicity by insisting that RCTs for the treatment of alpha-1 antitrypsin deficiency (AAT) with AAT concentrate showed no benefit for these patients. The PPTA's response to this allegation is on the

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Association's website at www.pptaglobal.org. The allegation is spurious and harms these patients' prospects of getting reimbursed treatment, which has been shown in ways more appropriate than RCTs to be effective. There are many ways to show efficacy for treatments—sticking to the dogma of "Just RCTs" harms patients.

And so, I continue to muse on Cheryl D'Ambosio and her family and hope that their courage will be rewarded with justice. The justice of a safe and efficacious treatment for Factor V deficiency. I noted during the WFH Congress the development of a Factor X concentrate by a British company. And a product for fibrinogen deficiency is already licensed in the U.S. These two diseases are as rare as Factor V deficiency. Hopefully, one day someone will stand up for Cheryl's Girls. (<http://www.mygirlsblood.com/>)

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