Translational Article

Special Issue on Drugs and Drug Metabolism

Drug Trials for Older People

Richard I. Lindley

George Institute for Global Health, Sydney, Australia.
Discipline of Medicine, Sydney Medical School, University of Sydney, Australia.

Address correspondence to Richard I. Lindley, Sydney Medical School, Westmead Hospital (C24), University of Sydney, Sydney, NSW 2006, Australia. Email: richard.lindley@sydney.edu.au

We are living in an era of unprecedented aging, with over a billion older people expected to be alive within a few decades. Despite this predictable demographic, drug trials have not kept pace with change and we now have significant evidence-practice gaps. These have arisen due to inappropriate age limits in randomized controlled trials and the near-universal exclusion of frail older people from studies. Suggested solutions include the abolition of age limits in new randomized controlled trials, and the routine measurement of frailty, with a new generation of randomized controlled trials to establish whether treatments remain effective and safe in old age and increasing frailty. We should all have a personal interest in ensuring that drugs used in our old age are truly effective.

Key Words: Randomized controlled trials—Aging—Frailty.

Received January 3, 2011; Accepted March 20, 2011

Decision Editor: Rafael de Cabo, PhD

BACKGROUND

The world population is aging, and health care is rapidly becoming “medicine for older people.” Unfortunately, despite best intentions, the pharmaceutical industry and the regulatory authorities have been stuck with the paradigm of testing new drugs in a younger fitter population and we now have significant evidence-practice gaps (1,2). For example, older people make up 63% of those with cancer in the United States yet represent only 25% of clinical trial participants (3). Our patients are frequently older frail people (4), exactly the sort of patients excluded from clinical trials (2). In this article, I will briefly review the global epidemiology of aging, discuss what sort of treatments we need to consider, provide examples of the effects of age on responses to treatment, review some of the major barriers in obtaining appropriate evidence, and finally suggest some solutions for the future.

AGING GLOBAL POPULATION

We are now living in an unprecedented era of aging. It has been estimated that the number of people aged 60 and older will triple in the least developed regions of the world by the mid-century (from 490 million to 1.59 billion) (5). In some countries, aging has an even more dramatic change; for example, in China, the number of people aged 80 years and older is growing at 5.4% a year, and this will result in an increase in the population aged 80 years and older from 8 million to more than 100 million within four decades (6). Similarly, India can expect to see some 324 million people aged 60 years and older by 2050. These changes have come about because infectious disease and undernutrition have largely been conquered in these countries.

Population aging has two main effects on health care; first, there are an increasingly large number of people who, by their mere survival, have developed chronic disease and who will benefit from drug treatment. Second, as this large cohort become increasingly frail and dependent on others for everyday activities, their risk of severe illness and death dramatically rises. The fundamental problem with drug treatment of older people is that the former population (old people with chronic disease) has been underrepresented in most clinical trials, and the latter (frail older people) nearly always excluded (2). Yet, these people are receiving a large number of medications, mostly in the absence of a robust evidence base. Although it might be appropriate to extrapolate the risks and benefits of drug regimes to those in old age (and the frail), there is just as much chance that we are doing harm. An example of the potential size of the problem is illustrated by the United Kingdom, with a population of 60 million, of whom more than 16% are aged 65 years or older, this results in some 10 million older people. About half a million frail older people in the United Kingdom live in residential care (nursing and residential homes), representing about 0.8% of the population, but some four times the size of the acute hospital
sector. In Australia, the proportional figures are remarkably similar with some 170,000 people living in institutional care out of a population of 21 million (7). Virtually, all these people will be receiving at least one drug each day, and 25% are using 4 or more concurrent medications a day (8).

**WHAT SORTS OF DRUGS DO WE NEED FOR OUR AGING POPULATION?**

It is worth considering the ideal trajectory for aging. Many would agree that remaining as healthy as possible for as long as possible, with a quick terminal illness, would represent the ideal. In other words, if we are to live with some degree of illness or frailty, this should be as short a period as possible (9). Many have argued that an ideal goal of gerontology research would be to reduce this period of disability but increase life expectancy—a concept known as compression of morbidity. Some, such as de Grey, have argued that substantial compression is an unfeasible goal as advances (eg, medication) that tend to extend life expectancy will probably also extend the life of those with frailty (the people at a much higher risk of death) (10,11). Although there is convincing evidence that compression of morbidity has occurred during the transition from very low-income countries to established market economies (12), evidence from the latter suggests that little or no compression of morbidity is now occurring (13). This raises the prospect of increasing life expectancy causing increasing time spent in a disabled state, which is a concern. It then follows that ideal drugs for older people should include those that either delay disabling or fatal events (or delay components of the frailty syndrome) or improve quality of life (when extending life expectancy is no longer a priority or feasible).

**Frailty**

Frailty is easily recognized, but there is currently no consensus on definitions. In a cross-sectional study of the Survey of Health, Ageing and Retirement in Europe (SHARE), frailty was operationalized by using the five components: exhaustion, shrinking, weakness, slowness, and low activity and by defining frailty as three or more of these components estimated prevalence rates of frailty ranging from 4% in the middle-aged (50- to 65-year olds) and 17% in those aged 65 years and older (4). Some other frailty indices have been purely physiological (14) and others a mix of very different variables (15). The challenge for those interested in frailty research is to achieve consensus on a useful definition.

**MEDICATIONS THAT EXTEND LIFE EXPECTANCY AND DELAY DISABILITY**

There are many effective nonpharmacological means to extend life expectancy and delay disability, such as an appropriate diet (low-salt low-fat diet and avoiding obesity), regular exercise, avoiding lethal habits such as smoking or other recreational drugs. However, although these are ideal public health interventions, realistically many are not achieved and thus drugs will be widely used (and promoted). Drugs such as antihypertensives, lipid lowering, and antithrombotic medication have all been shown to reduce the incidence of disabling or lethal cardiovascular conditions. Although the evidence base is robust for those in middle age, the evidence base becomes increasingly sparse for older people. Lipid lowering medication and antiplatelet therapies provide different examples of the problems of generating evidence for drugs for older people.

**AGE LIMITS AND LIPID LOWERING**

Age limits in clinical trials have been extremely common for all sorts of reasons and in general should not be routinely imposed. Biologically active treatments that are beneficial in young robust adults rarely reverse treatment direction purely due to chronological age. However, increasing comorbidity and a decreasing life expectancy can be expected to reduce the potential benefits of most treatments and will often, in parallel, increase adverse events. It follows that some treatments will cease to be worthwhile due to chronic disease accompanying aging or frailty. Surprisingly, we have virtually no data on when this occurs for most commonly used drugs, as the appropriate randomized controlled trials (RCTs) have never been performed. Many scenarios are possible: Mild degrees of frailty could increase the absolute benefits of some drug treatments, for example, statins for those frail with widespread vascular disease; conversely, moderate-to-severe frailty could reverse treatment directions, for example, a beneficial treatment for younger adults becomes harmful in the frail.

Age limits have sometimes been based on flawed reasoning. A good example is the widespread use of age limits in the statin trials. In this field, the observational epidemiology had a major influence in the design of cholesterol-lowering trials. For example, in the Framingham study, the epidemiological association between total cholesterol levels and coronary heart disease mortality was significantly positive in middle age (40–60 years old) but attenuated to be insignificantly positive at age 70 years and then insignificantly negative at age 80 years (16). This type of epidemiological observation was the basis of age limits of 75 years or less for all the major statin trials reporting in the 1990s. This was despite the authors of the original report stating that only a randomized controlled trial would settle the debate about cholesterol lowering in the older age group (16).

In the mid-1990s, the age limit of 75 years in the Heart Protection Study was lifted to 80 years, with no subsequent evidence of a difference between treatment effects in older versus younger patients (17). Indeed, major vascular events were reported in 142 (23.1%) of the simvastatin-allocated patients versus 209 (32.3%) of the placebo patients, \( p = .0002 \) in the subgroup of 1263 older patients (aged 75 years
and older) (17). The subsequent Cholesterol Treatment Tri-
lists’ meta-analysis of the Heart Protection Study and other
large statin trials confirmed the benefit of statin treatment in
the older age groups (see Table 1) (18). It is important to
note that in the Cholesterol Treatment Trials’ meta-
analysis, there was significant 12% relative reduction in to-
tal deaths (8.5% vs 9.7%, relative reduction 0.88 [95%
confidence interval 0.84–0.91]) (18). As only vascular
deaths were prevented, the effect of cholesterol reduction
on total deaths in old age will be dependent on the preva-
ience of vascular disease in the population being treated.
Studies in populations with a low risk of vascular death will,
in general, be underpowered to show any effect of choles-
terol lowering on total deaths. However, a recent report has
demonstrated that there are populations of older people
with very high levels of vascular disease, and in these popu-
lations, widespread use of statins are likely to have a public
health benefit (19). In the study of 85-year-olds from the
North East of England atherosclerosis, prevalence rates of
47% were reported (19).

Subsequent meta-analysis of the epidemiology of choles-
terol and ischaemic heart disease mortality has clarified the
role of cholesterol in old age and has confirmed the associ-
ation between cholesterol and ischemic heart disease into
old age but has also demonstrated that the association weak-
ens with increasing age such that a difference of 1 mmol/L
lower cholesterol was associated with a halving of ischemic
heart disease deaths for those aged 40–49 years old, de-
creasing to about a third lower for those aged 50–69 years old
to only about a sixth lower for the 70- to 89-year-old age group
(20). Hence, it is clear that statistically, it would be far more
difficult to demonstrate a mortality benefit of cholesterol low-
ering in the oldest old compared with a younger population,
despite the increased absolute risk of ischemic heart disease.

In summary, despite the association between cholesterol
and the risk of ischemic heart disease diminishing with age,
the clinical trial data have demonstrated that older people
can still benefit from treatment well into old age. An equally
important message is the requirement for extremely large-
scale meta-analyses to clarify the epidemiology and clinical
trial results. In fact, it has largely been the recognition of the
statistical issues in the epidemiology of cholesterol lowering
that has clarified the drug treatment in older people.

### Changing Risk Profiles in Old Age

Antiplatelet therapy provides a good example of how risk
changes with increasing age. The most recent meta-analysis
of the primary and secondary prevention trials with aspirin
has clearly demonstrated that the risks of aspirin increase
with age (21). In the secondary prevention trials, aspirin
benefits did not differ between older people and younger
people (those aged 65 years or older vs those aged 65 years
or younger). In the primary prevention trials, the risks of
occlusive vascular disease increased (as expected) with
increasing age but the meta-analysis also demonstrated that
the main risks of aspirin, namely hemorrhagic stroke and
extracranial bleeding, also increased with increasing age.
The strengths of these competing risks will clearly influ-
ence the net benefit of aspirin for primary prevention at
each age group. Given that the balance of risk and benefit
for primary prevention is very finely balanced, these
changes with age will result in a very unstable balance with
increasing age, especially as the meta-analysis found
other important risk factors that influenced the risks of
hemorrhagic stroke and extracranial bleeding. Therefore,
there remains great uncertainty of the balance of risks and
benefits of antithrombotic therapy for primary preven-
tion in old age.

### Barriers in Obtaining Evidence

Many of the barriers to participation in RCTs have been
discussed previously (1,22). A summary of the main bar-
riers and potential solutions are shown in Table 2. A few of
these require particular comment. It has been noted that
many information leaflets break readability recommenda-
tions, and long and complex documents are likely to be an

### Table 1. Major Vascular Event Rates Cholesterol-Lowering Studies: The Heart Protection Study and the Cholesterol Treatment Trialists’ Meta-Analysis

<table>
<thead>
<tr>
<th>Trial and Number of Participants</th>
<th>Age Subgroup of Interest (years)</th>
<th>Statin Allocated (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS (20,536)</td>
<td>≤65</td>
<td>16.9</td>
<td>22.1</td>
</tr>
<tr>
<td></td>
<td>≥65 to &lt; 79</td>
<td>20.9</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>23.6</td>
<td>28.7</td>
</tr>
<tr>
<td></td>
<td>≥75</td>
<td>23.1</td>
<td>32.3 (p = .0002)</td>
</tr>
<tr>
<td>CTT (90,056)</td>
<td>≤65</td>
<td>12.5</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>16.5</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Notes: CTT = Cholesterol Treatment Trialists, HPS = Heart Protection Study.

The control rates for major vascular events in the Heart Protection Study increase in each older age group from a rate of 22.1% in the 65-year-olds and younger to 32.3% in the 75 years and older age group. The lower event rate in the treatment group of the 75 years and older, compared with those aged 70 years and older, is probably a statistical issue where, by chance, the 75 and older subgroup did even better than expected on the statins.

### Table 2. Barriers and Solutions to Participation in Randomised Controlled Trials for Frail Older People (adapted from Ridda et al. [22])

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential commercial risk</td>
<td>Government funding for RCTs</td>
</tr>
<tr>
<td>Comorbidity excludes participants</td>
<td>Be inclusive, but measure frailty</td>
</tr>
<tr>
<td>Transportation limits research</td>
<td>Provide taxi fare or plan for home visits</td>
</tr>
<tr>
<td>Lengthy ethical and legal processes</td>
<td>Invest in high-quality trial materials and trial design</td>
</tr>
<tr>
<td>Relatives act as “gatekeepers”</td>
<td>Encourage appropriate consumer involvement</td>
</tr>
<tr>
<td>High mortality rate</td>
<td>May be an advantage for some interventions (great scope for benefit)</td>
</tr>
<tr>
<td></td>
<td>May need to substantially increase sample size to allow for increased dropout for other interventions</td>
</tr>
</tbody>
</table>

LINDLEY ET AL.
even greater barrier for older people who find reading more difficult or may have cognitive impairment (23). The use of simple language, and consumer involvement, can dramatically improve trial materials (24).

Some very simple trial practicalities can make a big difference to patient recruitment such as a budget for providing taxi transport to attend a research clinic or assessing people in their own home. It may also be important to include people who are mentally incompetent, for example, interventions for the noncognitive symptoms of dementia, and appropriate resources need to be spent on developing appropriate patient and carer trial materials in preparation for the legal and ethical requirements for such RCTs.

The commercial sector is the increasingly dominant commissioners of drug research, and the commercial imperative is for drugs that can be patented and provide a financial return for the company. Trials that evaluate a generically available drug, while having potential merit, are not commercially viable, yet most available drugs (many off-patent) have not been adequately tested in older frail populations. As adverse events are more common in old age (and in frailty), drug companies have an incentive to avoid such populations, as subsequent RCTs in older people could give their product a bad reputation. In addition, medicine is moving at an incredibly fast pace. New treatments may make older treatment strategies obsolete. For example, Bajen and colleagues (21) have suggested that in the era of generic statin availability, aspirin may not have a place in the primary prevention of cardiovascular disease, as statins are likely to be safer and be more cost-effective. The older person today is certainly different from the older person from a few decades ago, and this background change in epidemiology could also shift the balance of risk and benefits within a few decades. In countries with a public-funded health system, it would seem essential to ensure that large RCTs of promising interventions (particularly generically available drugs) are funded, in particular for older people.

**Be Inclusive but Measure frailty**

The main reason older frail people are excluded from RCTs is the frequent incorporation of exclusion criteria that feature medical problems that are increasingly common in old age, such as renal impairment, cardiovascular disease, and functional impairment. These are common components of the frailty syndrome, and thus, the key issue of exclusion is because of frailty. Hence, the management of frailty in RCTs is the key solution to the problem. As discussed previously, frailty is a useful term to describe people at risk of poor health outcomes (25), despite the lack of a standardized definition. Patients in Aged Care Facilities and those in hospital departments of geriatric medicine are typical of older people at high risks of poor outcome due to frailty. In addition, there are many more frail older people living in the community (4). It is somewhat ironic that our success in public health and medical care has led to a large number of older frail people, yet their current medical care is severely handicapped by the exclusion of the frail from most medical research. If we are to reliably improve the care of the frail older person, this must change but how? The old paradigm of establishing inclusion and exclusion criteria to generate a homogenous population is redundant in this situation. Frailty is heterogeneous, as decades of different environmental conditions, infections, degeneration, and underlying genetics have created an infinite different ways of making you frail. One proposed solution is to estimate frailty, with the assumption that similarly frail individuals (from whatever cause) may have similar responses to interventions. This is only likely to be true if that measure of frailty has been shown to be associated with similar outcomes for similar degrees of frailty. An example of a well-validated approach is the measurement of accumulated deficits (15). In this approach, a simple binary (Yes/No) measure is taken of a large number of deficits, and the advantage of this approach is its simplicity and the ability to accept self-reported responses. This Frailty Index has been shown to not only predict mortality but also institutionalization. It therefore measures important aspects of vulnerability, which are particularly relevant for the older person, and thus may be a useful additional baseline variable to collect in new RCTs of management or treatment strategies. The Box 1 illustrates the components of the Frailty Index utilized in a vaccination trial (26). It is important to note that the precise constituent items are not as important as having a sufficient number of different deficits. It is the accumulation of deficits that are important for this scale. In preliminary results, frailty was found to be associated with the immune response to vaccination (26). It is likely that many, if not most medical treatments, will have an association between the balance of risks and benefits and frailty. For many interventions, the reduced efficacy and increased risk of adverse events will render commonly used treatments futile or even harmful. However, the increased risk of death and dependency for those with increased frailty identifies those at increased absolute risk and it is feasible that some interventions will be particularly effective for this group. Until the relevant RCTs are performed, we simply will not know in which category most commonly used drug treatments will fall. It is also uncertain at this stage, whether any interventions could improve overall frailty, as defined by the “accumulation of deficits” method.

Many other frailty scores have been suggested but none, as yet, have been shown to have superiority over the other. As they cover a large variety of domains in different proportions, it is unlikely that consensus will be reached in the short term. However, if treatments are likely to be used in older frailer populations (eg, anticoagulants, blood pressure treatments, cholesterol-lowering treatments, sedatives, and antipsychotics, antibiotics, antidepressants), it is imperative
As health care rapidly becomes health care of older people, we must start to invest in research that identifies effective from ineffective treatment, especially as frailty accumulates. Those countries with public health services need to invest a proportion of the health service budget in such research as the commercial sector may not choose this type of investment due to the risk of identifying adverse events for their market-leading drugs. My prediction is that these new trials will identify that many currently routine treatments are ineffective or harmful, and subsequent disinvestment in these interventions will help afford the truly beneficial interventions. This will be one strategy of being able to afford our aging populations and a strategy that most would support, given we all have a personal interest in getting this right.

References
8. AIHW. Use of Health and Aged Care Services; Older Australia at a Glance. In: *Welfare AIoHa, ed. Canberra, Australia: Australian Government.


