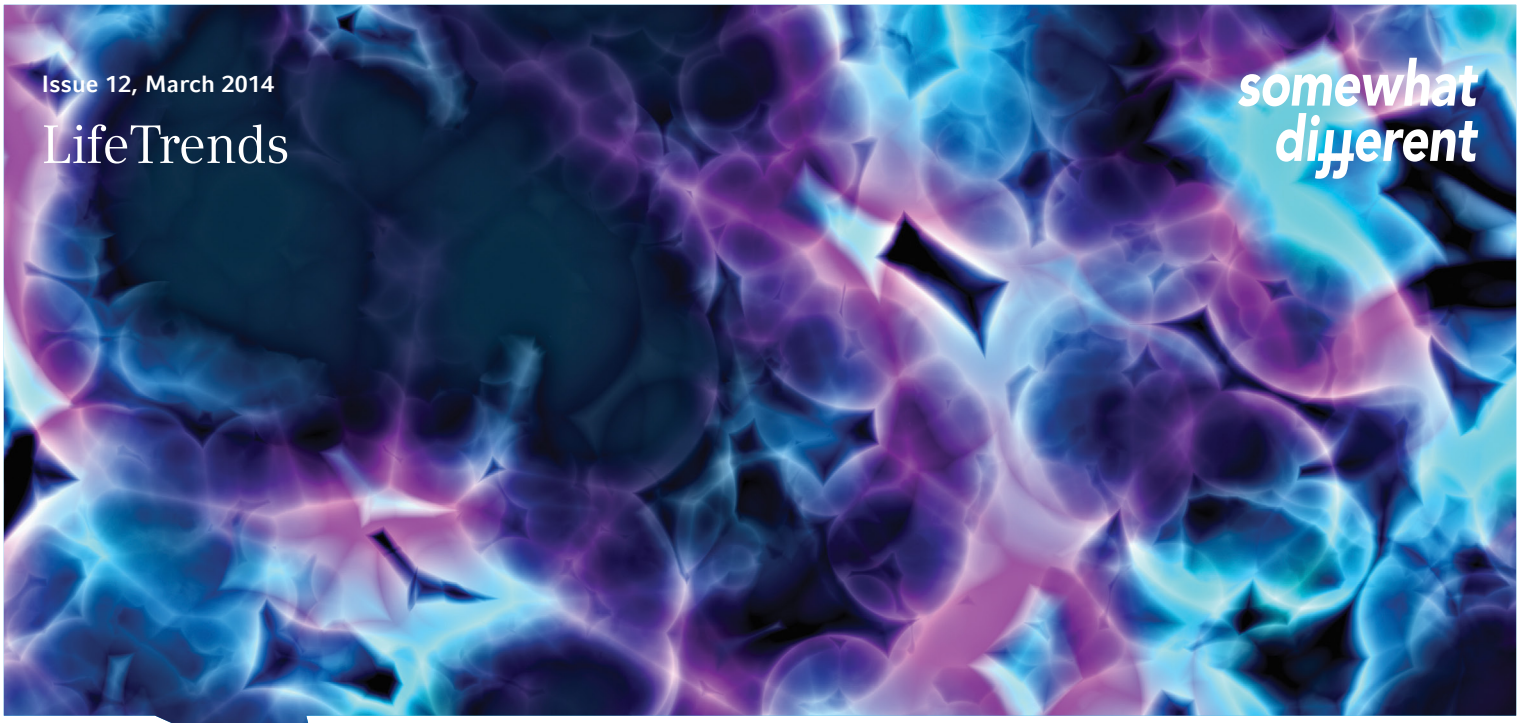
Issue 12, March 2014
LifeTrends
somewhat different



Autophagy is an evolutionarily conserved stress response that is present in all living cells

Autophagy: An Unsung Hero

In recent years there have been major advances in our understanding of very specific cellular processes, and how they work to keep cells healthy. Pharmaceutical research scientists are working hard, attempting to harness them, to develop commercially viable drugs. On the other hand, simple non-commercial methods of activating them get little attention. In this article we will discuss a very ancient (yet recently discovered) cellular repair pathway and its connection to diet.

Apoptosis, which was first described in 1842, has occasionally made medical headlines. The word, derived from Greek, roughly translates to "falling off". Apoptosis is defined as "the process of programmed cell death that may occur in multicellular organisms". Unlike cell death by necrosis, apoptosis is a relatively civil affair. Cellular signaling calls in macrophages to clean up the mess, leaving no trace of the cell and causing none of the damage that necrotic cells do. It is estimated that in the average adult between 50 and 70 billion cells quietly die each day by apoptosis!

Apoptosis plays many roles. For example, the differentiation of fingers and toes in a developing human occurs because cells between the fingers apoptose. It also plays a role in preventing cancer: there are mechanisms that detect fatal genetic errors in cells. To protect the rest of your multicellular republic, such defective cells exhibit the apoptotic response and commit suicide. Clearly, the inactivation of apoptosis is central to the development of cancer. In fact, numerous cancer therapies attempt to reactivate the apoptotic response in cancerous cells.

It turns out that apoptosis has a cousin that hasn't had its share of the limelight: Autophagy. It too translates from Greek, and means "self eating". Despite sounding sinister, autophagy plays a very important role in maintaining cellular order. Whilst we can trace its roots back more than 3 billion years, we've only been able to understand its mechanisms for about 15. Where apoptosis terminates delinquent cells, autophagy plays a role in preventing them from becoming ungovernable in the first place. From a multicellular organism's perspective both autophagy and apoptosis promote the health of the cellular republic. From a citizen cell's perspective autophagy, unlike apoptosis, promotes life rather than death.

Autophagy can be defined as "the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes." It is an evolutionarily conserved stress response that is present in all living cells. Nutrient stress (i.e. a shortage of nutrients) is one of its most potent activators. Part of its role is to scavenge cells, in search of damaged proteins and organelles for recycling, thus putting the building blocks of life to better use. This has the obvious health benefit of eliminating damaged cell components that may go on to later impair the functioning of the cell and lead to disease in the republic of cells. From the scientific literature we find that autophagy protects

against genomic instability giving it a key role in preventing diseases such as cancer, neurodegeneration, cardiomyopathy, diabetes, liver disease, autoimmune diseases and infections. Sounds important!

The evolutionary purpose of a cellular self-repair and recycling mechanism is obvious: during periods of protein deficiency, the cell will nevertheless require some basic amino acid building blocks to ensure it can continue to function. Selectively degrading misfolded proteins and damaged organelles for this purpose makes sense, serving a double benefit: it removes cellular junk, and provides much needed nutrients during times of nutrient shortage. Nature would long ago have weeded out cells that indiscriminately tried to recycle any random cellular component, even if it still functioned well. At least two systems are involved in this recycling process: Autophagy (which we discuss here) and the ubiquitin-proteasome system (which we don't).

Autophagy explains quite elegantly why caloric restriction has life extension benefits in all model animals that have been studied. Reducing caloric intake is now known to activate autophagy, and based on the discussion above would be expected to clean out cellular garbage, so to speak, and promote health. Indeed, a fascinating 2007 paper titled "Autophagy is required for dietary restriction-mediated life span extension in C. elegans" puts forward that caloric restriction does not work without autophagy [1]. This suggests that autophagy is caloric restriction's primary mechanism of action.

What then is the primary regulator of autophagy? The pharmaceutical industry is naturally working hard to find novel patentable compounds that regulate it and why would they do otherwise? They are beholden to their shareholders. It turns out that one widely unnoticed cellular signalling pathway is a major regulator of autophagy. This pathway is called mTOR, or the Mechanistic Target of Rapamycin. This ancient pathway is common to all living cells and can be traced right back to the LECA or the Last Eukaryotic Common Ancestor, mother to most living cells today.

Reducing caloric intake is now known to activate autophagy

1 Jia K and Levine B, 'Autophagy is required for dietary restriction-mediated life span extension in C. elegans', Autophagy, 2007 Nov-Dec; 3(6):597-9

Bio-prospecting is defined as the search for plant and animal species from which medicinal drugs and other commercially valuable compounds can be obtained. In 1964 a group of Canadian scientists went bio-prospecting to the Easter islands. They brought back a soil sample containing a bacterium. This bacterium produced an antifungal molecule, later called Rapamycin, that proved to have a range of fascinating and profound biological effects in a variety of cell types. These effects lead to the question: what is the target of rapamycin? When they found it, they unimaginatively named it the Target of Rapamycin (TOR). In the intervening years we have come to appreciate that the TOR complex has much more to it than just Rapamycin, and in that sense the name is misleading and unfortunate.

In the last 15 years or so TOR research has exploded. In the same way that the Insulin/Insulin-like Growth Factor cell signalling pathway is the primary nutrient sensing pathway for glucose, TOR is the primary nutrient sensing pathway for amino acids. It turns out that an abundance of amino acids up-regulates TOR which reduces autophagy while simultaneously encouraging cell division. This makes sense: cells should divide more readily when there is an abundance of nutrients.

Autophagy promotes good health at a cellular level by basically taking out the garbage. And autophagy is largely regulated by mTOR. So the crucial question is: What regulates mTOR? As is alluded to above, mTOR is controlled predominantly by diet. Specifically the protein and carbohydrate content. A diet high in either of these will up-regulate mTOR and reduce healing autophagic activity. Interestingly, fat in the diet does not affect mTOR. Ron Rosedale, MD and internationally renowned expert in aging and metabolic disease, has for years been advocating a health promoting diet. Rosedale, Westman & Konhilas have authored a paper titled "Clinical Experience of a Diet Designed to Reduce Aging"[2]. In this paper they show that people who follow Rosedale's diet develop a metabolic profile that is similar to that of centenarians.
He has had astonishing results in his patients, treating them only with diet: specifically a high fat / adequate protein / very low carbohydrate diet. Rosedale has been promoting this way of eating since as far back as Atkins has, the crucial difference being that Atkins ignored the perils of excess protein. Developments in aging research over the last two decades have largely vindicated Rosedale's original work, which now looks almost prophetic. People on his diet experience all the benefits of caloric restriction, without actually restricting calories.

If you are curious, and would like to know more about autophagy, mTOR, and Rosedale's ideas that discuss them then the web is a great resource. PubMed also contains numerous papers discussing autophagy and mTOR, however, sadly, most of them focus more on patentable compounds rather than on the role and influence of diet.

Author

Jordi Posthumus
Vice President – Longevity Trading
Hannover Life Re Bermuda
Tel: +1 441 279 1150
jposthumus@hlr.bm

2 Rosedale R, Westman EC and Konhilas JP, 'Clinical Experience of a Diet Designed to Reduce Aging', The journal of applied research, 01/2009; 9(4):159-165.

When the Gain is Toxic

Steady levels of anabolic steroid misuse within the general population can have implications for risk management

Mortality and morbidity risks associated with substance misuse have long been recognised. Risk product providers attempt to mitigate these risks by identifying lives with a current or former history of substance misuse during the risk selection process. This enables them to apply substandard ratings or decline cover altogether in more serious cases.

The process of identifying at-risk individuals generally begins with a positive disclosure in response to questions about substance use within application forms or question sets of point of sale solutions. Such questions typically focus on recreational drugs, in particular psychoactive drugs, such as cannabis, ecstasy, heroin and cocaine.

One class of drug seldom asked about is anabolic androgenic steroids. This is despite steady levels of use among young-to-middle aged males: usually the demographic most likely to hold life insurance.

We recommend that anabolic steroids, as they are colloquially known, should be included alongside other drug examples in application forms and point of sales question sets. This practice should assist in identifying more lives who engage in non-prescribed use that don't necessarily regard themselves as drug misusers.

Legitimate medical application

Anabolic steroids are a group of substances that includes the male sex hormone testosterone along with numerous synthetic derivatives. Their primary action is to build muscle or promote androgenic effects (masculine characteristics). They may be administered orally, parenterally (i.e. via intramuscular or subcutaneous injections) or in the form of skin patches.

Recently their clinical utility has included the treatment of cachexia (wasting syndrome, often associated with chronic disease), delayed puberty, male hypogonadism (diminished functional activity of the testes) and, to a lesser extent, suppression of lactation, loss of libido following pregnancy or menopause, metastatic breast cancer, osteoporosis, endometriosis and hereditary angioedema (an inherited blood disorder), as well as certain anaemias and growth disorders. Therapeutic doses are often designed to replace or mimic normal physiological testosterone levels.

Medically prescribed anabolic steroids, however, account for only a small proportion of use. Far greater use, or misuse, is reported amongst recreational body builders, amateur sportsmen, body-conscious youths and young adults, and within certain occupations.

Changing user profile

In recent years there has been a significant epidemiological shift in the type of individuals using non-prescribed anabolic steroids. Their use is no longer confined to elite professional athletes and people regularly involved in competitive sports. There has been a marked increase in use by those simply seeking to enhance their personal appearance. It has been reported that as many as 15-30% of current users do not participate in any regular sport[1].

Such 'cosmetic doping' may be linked to media-driven shifts in cultural perceptions of masculine and feminine stereotypes. These may also have contributed to the emergence of a form of body dysmorphia. An obsessive focus on muscular appearance (muscle dysmorphia) can deflect conscious attention from other psychological issues and underlying conflicts.

Anecdotally, it seems anabolic steroid misuse is also more common in occupations that involve exposure to some level of hostility, where an increased physical presence can be advantageous. There is some evidence of anabolic steroid misuse among females, but markedly less so than among males.

Evidence from around the world regarding anabolic steroid use in different age groups varies. Data is available in the UK from the National Institute for Health and Care Excellence (NICE), with recent publications citing that up to 70,000 people aged between 16 and 59 in England and Wales were thought to have injected anabolic steroids. Although data regarding anabolic steroid use in South Africa is not as readily available, a couple of studies by Lambert et al were done in the 1990s looking at the prevalence of anabolic steroid use in adolescents.

Their 1998 study found a prevalence of 14.4 users per 100,000 people[2]. Similar studies done in the US, Canada, and Sweden have also reported anabolic steroid misuse in adolescents comparable to that seen in South Africa. Clearly more research is required in this area, particularly looking at the prevalence of anabolic steroid misuse in adult populations likely to buy insurance.

Administration

Non-prescribed use often involves increasing doses over a number of weeks or months, known as 'build-up cycles', followed by intervals of complete abstinence. These intervals are designed to minimise side-effects and allow some downtime for the receptors to which steroids bind. Cycles may also include 'stacking', where more than one steroid is used to avoid acquiring tolerance, and 'pyramiding', which involves a regimen of escalating anabolic steroid dosing. Non-prescribed doses can sometimes be 10 to 100 times greater than therapeutic doses.

Adverse effects

Not surprisingly, we have limited data on lives with a history of medically unsupervised anabolic steroid use, and direct evidence linking anabolic steroid misuse to a wide range of complications has yet to be definitively established. However, numerous side effects have been reported. Many of these are dose-related and reversible once drug use has ceased. Unfavourable manifestations reportedly range from acne and male pattern baldness to isolated stroke, myocardial infarction and cardiomyopathy.

Detrimental effects have been noted in, but are not limited to, the following systems: cardiovascular, hepatic, reproductive, urinary, endocrine, musculo-skeletal, mental health and dermatological. Evidence of anabolic steroid-related complications or side effects at application, particularly following a period of discontinuance, should be regarded cautiously during the risk assessment process as many complaints should resolve within months.

Risk management considerations

Identifying lives with a history of previous or current anabolic steroid misuse usually relies on individual disclosure as formerly mentioned.

1 Quaglio G et al., 'Anabolic steroids:dependence and complications of chronic use', Internal Emergency Medicine, 2009, 4:289-296

2 Lambert, M.I, Titlestad S.D, Schwellnus M.P. Prevalence of androgen-anabolic steroid use in adolescents in two regions of South Africa, S Afr Med J. 1998 Jul;88(7), pp 876-80

Although there are several physical stigmata suggestive of anabolic steroid misuse, it is important to remember that these are very non-specific and misuse is highly unlikely to be detected based on the medical attendant's examination report. The more likely scenario is where misuse is suspected based on the holistic assessment of an application, which leads to closer scrutiny of the medical attendant's clinical findings, looking for the following clinical signs:

- Hypertension
- Gynaecomastia (enlarged breast tissue) in men; breast tissue atrophy (shrinking) in women
- Increased body mass index, with special reference to muscular build.

As mentioned above, none of these findings are specifically unique to anabolic steroid misuse and their presence should be contextualised according to the full medical profile.

Similarly, abnormal lab results on standard insurance blood tests or abnormal electrocardiograms which could suggest anabolic steroid misuse may also be attributed to other causes. Below is a table highlighting the commonest and most likely available abnormal laboratory test results that may indicate anabolic steroid misuse:

Test	Likely result with anabolic steroid misuse
ALT (alanine aminotransferase)	Elevated
AST (aspartate aminotransferase)	Elevated
LDH (lactate dehydrogenase)	Elevated
CK (creatine kinase)	Elevated
LDL (low density lipoprotein)	Elevated
HDL (high density lipoprotein)	Decreased
RCC (red cell count)	Elevated
Hb (haemoglobin)	Elevated
Hct (haematocrit)	Elevated

Ventricular hypertrophy (thickening of the ventricular walls in the heart) as indicated on electrocardiograms could also suggest anabolic steroid use.

Individuals who misuse anabolic steroids rarely seek professional medical help for minor associated problems. They may also not regard themselves as drug misusers and frequently assume their doctor will know little about anabolic steroids. This suggests that GP reports obtained during the risk selection process may sometimes offer little or nothing of relevance.

Where the route of administration involves injected anabolic steroids, there are additional risk factors to consider. These include the development of bacterial abscesses, septic arthritis, septicaemia and transmissible infections such as HIV and viral hepatitis. Prudent practice would suggest acquiring HIV and hepatitis B & C serology alongside any history of injected anabolic steroids. Some commentators also see the use of non-prescribed anabolic steroids as a potential gateway to other forms of substance misuse.

A Swedish study by Skarberg and Co. published in 2009 examined the association between anabolic steroid misuse and polysubstance dependence, and reported that many of the subjects interviewed also took other drugs of abuse. Eighty-one percent had used cannabis, 78% had used amphetamines, and 25% heroin. Around 50% also drank alcohol to hazardous or harmful levels[3]. The study also found that anabolic steroids were frequently combined with other hormones, pharmaceuticals and dietary supplements.

Despite the small sample size of this study, and an apparent selection bias in the recruitment of subjects, we may conclude that some anabolic steroid misusers also use other drugs of abuse, pharmaceuticals and dietary supplements. Users may take these to consolidate the effects of steroids, to manage unwanted side-effects, to avoid detection via testing or to improve sleep. In some cases their use may simply be indicative of increased risk-taking behaviour.

Supplementary questions or questionnaires requesting, among other details, evidence of polysubstance use with any disclosure of anabolic steroid misuse may be useful during the risk selection process.

3 Skarberg K et al., 'Multisubstance Use as a Feature of Addiction to Anabolic Androgenic Steroids', European Addiction Research,2009; 15:99-106

A further risk assessment consideration is the potential role of anabolic steroids in masking or concealing undisclosed or occult illnesses. In such cases it can be virtually impossible, even with the benefit of GP's reports, for an underwriter to recognise when an applicant is going to extraordinary lengths to disguise an underlying illness.

Psychological impacts have also been reported in some of those misusing anabolic steroids, but causal links have yet to be established. Reports of hyperactivity, anger, irritability, anxiety, mania and hypomania are all noted in the literature.

The term 'roid rage', first coined in the 1980s, describes psychotic-type episodes, often involving violence, allegedly resulting from the influence of anabolic steroid misuse. Homicidal behaviour and, more commonly, depressive syndromes with a risk of suicide have also been documented. Where a history of acute mental health issues is disclosed on application, particularly by young adult males with no identified precipitants, it would certainly not be unreasonable to consider possible anabolic steroid misuse.

There has also been research regarding the risk of reusing anabolic steroids and other substances based on recent or current use. A small study conducted in Australia examined 214 exercising males between the ages of 16 and 61 predicting the future anabolic steroid use intentions based on their current substance use. The study found that 16% of this sample indicated that they would use anabolic steroids in the future. The most important driver of this intention appeared to be to improve personal appearance[4]. Despite the small sample size, this is an important aspect for underwriters to consider when underwriting applicants with a recent history of anabolic steroid misuse.

Other factors that influence individuals to reuse anabolic steroids include the psychic and physical addiction that results in adverse withdrawal side-effects upon discontinuation of the drugs (such as depression, fatigue, paranoia and suicidal thoughts and feelings). Interestingly, it was found that these psychoactive effects and withdrawal symptoms (as well as the biological mechanisms) of anabolic steroids appear to mirror the mechanisms and complications accompanying cocaine, alcohol or opioid abuse.

Anabolic steroid use is no longer confined to elite professional athletes and people regularly involved in competitive sports

Furthermore, a strong desire to continue anabolic steroid misuse exists in the face of negative consequences i.e. the drugs are continued in order to provide on-going perceived positive effects and to inhibit withdrawal effects. It has also been suggested that a portion of anabolic steroid abusers may develop a sex-steroid hormone dependence disorder [5].

Summary

There are currently no defined treatment protocols for anabolic steroid misuse. Abstinence is the ultimate treatment goal, we would recommend considering insurance terms following a period of discontinuance to avoid potential user relapse, possible withdrawal syndrome and resolution of the many associated side effects.

4 Dunn, M, Mazanov, J, Sitharthan, G. Predicting future anabolic-androgenic steroid use intentions with current substance use: findings from an internet-based survey, Clin J Sport Med. 2009 May;19 (3) pp222-7

5 Kischner, M.D, Griffing, M.D, Anabolic Steroid Use and Abuse. Medscape, 8 Mar 2013

At Hannover Re Africa, we will consider terms for life after 12 months of abstinence and living benefits following a minimum period of 24 months' abstinence provided that there is evidence to support that there are no significant adverse side-effects associated with the steroid misuse.

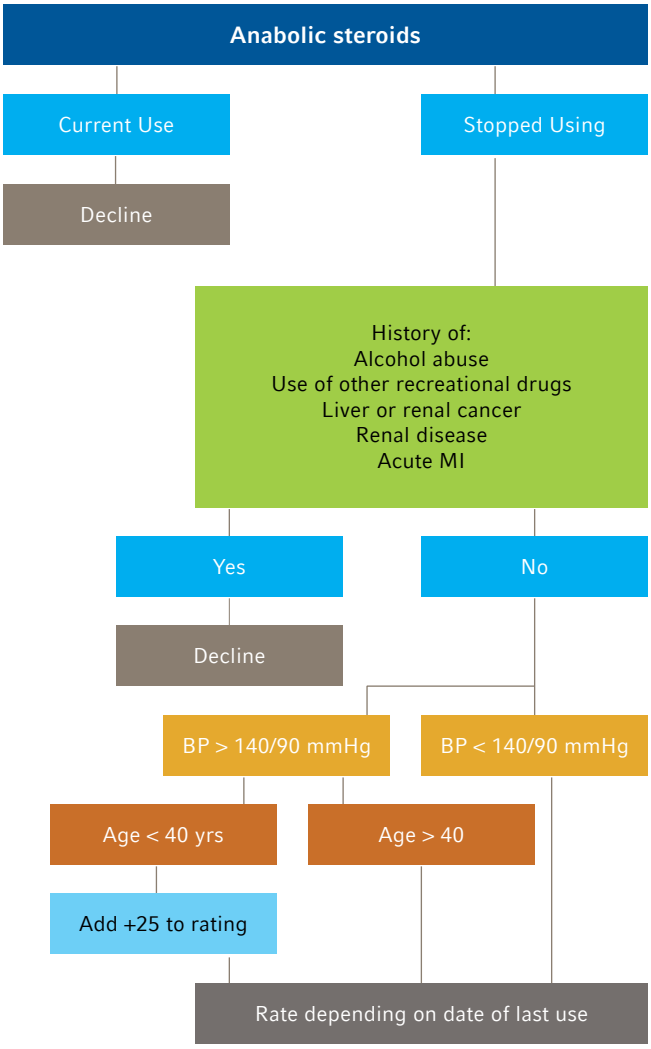
The long-term outlook for anabolic steroid users depends on numerous variables including current versus past use, route of administration, prescribed versus non-prescribed use, concomitant polysubstance use, and development of complications or side effects.

Risk product providers may wish to give some thought to including anabolic steroids as an example drug type as part of recreational drug questions in application forms and point of sale solutions.

If you would like to know more about this topic, please contact your Hannover Re representative.

Author

Craig Butler
Manager: Underwriting & Claims Strategy
Hannover Re UK Life Branch
Tel: +44 1344 84 6823
Craig.Butler@hannover-re.com



Hannover Re Africa's underwriting guidelines in cases with current or previous use of anabolic steroids (as per Ascent guidelines and rating tables)

Published by
Hannover Re Group Africa (Pty) Ltd.
Tel. +27 11 481-6783
lifetrends@hannover-re.co.za
Hannover Re House, Corner Hillside and Empire Roads, Parktown, Johannesburg, 2193. All rights reserved.