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ΑΡΧΕΙΑ ΕΛ.Ε.Φ.Ι.

Ελληνική Εταιρεία Φαρμακευτικής Ιατρικής

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ΔΙΑΒΑΣΤΕ ΣΕ ΑΥΤΟ ΤΟ ΤΕΥΧΟΣ:

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Αγαπητοί συνάδελφοι,

Έργο της ΕΛΕΝΗΣ ΖΟΥΝΗ, 2010, 125x125, μελάνια, γραφίτες σε ξύλο.

Στο τεύχος του Δεκεμβρίου 2013 σας προσκαλώ να διαβάσετε τα άρθρα μας και να σκεφθείτε πώς μπορείτε να ενισχύσετε την επιστημονική συζήτηση και ερευνητική σκέψη που επιχειρούμε να διεγείρουμε. Στο παρόν τεύχος παρουσιάζεται επίκαιρη αναφορά σε νέο τύπο κλινικής μελέτης και με μεστό τρόπο περιγράφεται η εξέλιξη στον κλινικό ερευνητικό ιστό με 3 σύντομες δημοσιεύσεις σχετικά με την διαχείριση επιτήρησης των προγραμμάτων, ενώ με εκτεταμένη βιβλιογραφική τεκμηρίωση ανασκοπείται η διαδικασία της γήρανσης και με εξωστρεφή διάθεση σχολιάζεται η διεύρυνση του καταστατικού της ΕΛΕΦΙ, που προβλέπει πλέον την εγγραφή και δράση ως μελών μας, επιστημόνων της Φαρμακευτικής Ιατρικής απασχολουμένων, εκτός της Φαρμακοβιομηχανίας, σε Ερευνητικά, Ακαδημαϊκά ιδρύματα, στο ΕΣΥ και στις Αρχές Υγείας.

Καλωσορίζουμε κάθε συνάδελφο με ενδιαφέρον στην προσφορά για την ανάπτυξη της Φαρμακευτικής Ιατρικής στη χώρα μας.

Σκεφτόμενη δε ευρύτερα, τολμώ να επεκτείνω την πρόσκληση για διάλογο και αλληλεπίδραση και σε επιστημονικές εταιρείες κοινού ενδιαφέροντος για την έρευνα και τεχνολογία στην υγεία, ώστε με την παράθεση και αντιπαράθεση ιδεών και απόψεων να προχωρήσουμε στην παραγωγή γνώσης, εκπαίδευσης και έρευνας στο πεδίο της Φαρμακευτικής Ιατρικής.

Με τη συναίσθηση της προσφοράς στη δημόσια υγεία, με ανθρωποκεντρική φιλοσοφία και με εφόδιο την εξειδίκευση της φαρμακευτικής ιατρικής, διευκολύνουμε το σχετικό διάλογο με την ανοικτή πρόσβαση “open access” στο περιοδικό μας, τα Αρχεία Ελληνικής Εταιρείας Φαρμακευτικής Ιατρικής, χωρίς κόστος για τους αναγνώστες μας.

Για τη διατήρηση και ενίσχυση της έκδοσης αλλά και των τακτικών επιστημονικών-εκπαιδευτικών συναντήσεων & δράσεων, θα ήθελα να ζητήσω την έμπρακτη συνδρομή σας οικονομική και προσωπική. Για το λόγο αυτό, πέρα από τη διάδοση του περιοδικού σε συναδέλφους του περιβάλλοντος σας, επιπρόσθετα στο περιοδικό δεχόμαστε εταιρικές καταχωρήσεις και εκπαιδευτικές επιχορηγήσεις και σε περίπτωση ενδιαφέροντος παρακαλώ να επικοινωνήσετε μαζί μας.

Κλείνοντας ευχαριστώ τους φίλους του περιοδικού καθώς επίσης τους συγγραφείς και φυσικά τα μέλη της συντακτικής επιτροπής.

Με την ευκαιρία των εορτών, εύχομαι **Χρόνια πολλά με Υγεία και δημιουργική διάθεση. Καλή Ανάγνωση & Καλή Χρονιά!**

Βαρβάρα Μπαρούτσου

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* Στην ΕΛ.Ε.Φ.Ι. συμμετέχουν ως μέλη ιατροί, φαρμακοποιοί ή πτυχιούχοι βιολογικών επιστημών, οι οποίοι ασχολούνται με κλινικές μελέτες (έρευνα), φαρμακοεπαγρύπνηση, εγκρίσεις φαρμάκων και με άλλους τομείς της Φαρμακευτικής Ιατρικής.

Το νέο καταστατικό της ΕΛΕΦΙ αποτελεί ένα μοναδικό εργαλείο για την ανάπτυξη της Φαρμακευτικής Ιατρικής στην Ελλάδα

Κατερίνα Παπαθωμά,
Πρόεδρος ΕΛΕΦΙ

Η Ελληνική Εταιρία Φαρμακευτικής Ιατρικής ιδρύθηκε το 1991 ως αποτέλεσμα μιας πρωτοβουλίας συναδέλφων-στελεχών της Φαρμακευτικής Βιομηχανίας. Η χρονική περίοδος που ιδρύθηκε η ΕΛΕΦΙ συνέπεσε με την ταχεία ανάπτυξη της φαρμακοβιομηχανίας στη χώρα μας. Η ανάπτυξη αυτή δεν θα ήταν δυνατή χωρίς την καθοριστική συμβολή των Ιατρικών/Επιστημονικών τμημάτων τα οποία κατάφεραν να υποστηρίξουν με επιστημονικά δεδομένα και κλινική έρευνα, την ασφαλή και αποτελεσματική χορήγηση των φαρμάκων στη χώρα μας.

Η ΕΛΕΦΙ από την ίδρυσή της μέχρι και σήμερα, με την βοήθεια των μελών της, έχει συμβάλλει ουσιαστικά στη διαμόρφωση του απαραίτητου ρυθμιστικού πλαισίου για την διεξαγωγή της κλινικής έρευνας στη χώρα, ενώ παράλληλα υποστήριξε τα μέλη της με κάθε τρόπο, (εκπαίδευση, ανταλλαγή απόψεων, διαμόρφωση προτάσεων, επαφές με αρμόδιους φορείς, κλπ) στο δύσκολο έργο τους στο πλαίσιο της φαρμακευτικής βιομηχανίας.

Οι συνθήκες αλλάζουν

Τα τελευταία χρόνια χαρακτηρίστηκαν από μια σημαντική ανάπτυξη της φαρμακευτικής έρευνας που είχε σαν αποτέλεσμα την παραγωγή νέων καινοτόμων φαρμάκων ενώ παράλληλα, ένας μεγάλος όγκος επιστημονικών πληροφοριών προστέθηκε στον τομέα της Φαρμακευτικής Ιατρικής (ΦΙ). Το επιστημονικό πεδίο της ΦΙ διευρύνθηκε ως αποτέλεσμα της πολυποίκιλης ανάπτυξης της φαρμακευτικής έρευνας, ενώ περισσότερες ειδικότητες επιστημόνων, πέραν των ιατρών, φαρμακοποιών και βιολόγων, μετέχουν πλέον στην ανάπτυξη του αντικειμένου της Φ.Ι.

Σε εθνικό επίπεδο, από το 2009 βιώνουμε ένα διαρκώς μεταβαλλόμενο εξωτερικό περιβάλλον ως αποτέλεσμα της μετακίνησης της στόχευσης από την ανάπτυξη στον έλεγχο των δαπανών στους τομείς της φαρμακευτικής πολιτικής. Στις συνθήκες αυτές, η συνεννόηση όλων των παραγόντων τόσο στο δημόσιο όσο και στον ιδιωτικό τομέα, αναδεικνύεται ως η πρωταρχική ανάγκη. Παραδείγματα θεμάτων συνεννόησης υπάρχουν πολλά με πιο πρόσφατα τη βελτίωση του πλαισίου διεξαγωγής των κλινικών μελετών, καθώς και τη συζήτηση σχετικά με την πρόσβαση των ασθενών στα φάρμακα και με τα προγράμματα Εκπαίδευσης & Υποστήριξης Ασθενών.

Η Φαρμακευτική Ιατρική αποτελεί τον συνδετικό κρίκο και το πεδίο συνεννόησης όλων των επιστημόνων/παραγόντων που δραστηριοποιούνται στα πολλαπλά αντικείμενά της ανεξάρτητα από τον χώρο στον οποίο κινούνται επαγγελματικά (δημόσιο ή ιδιωτικό τομέα).

Οι ανάγκες αυτές λοιπόν εξυπηρετούνται με τον καλύτερο δυνατό τρόπο μέσα από τις αλλαγές που εισάγονται με το σχεδόν καινούριο καταστατικό της ΕΛΕΦΙ (ΔΔΔ του Ταμείου Νομικών Αρ. Φύλου 9569/13.09.2013)

Η μεγάλη μας φιλοδοξία είναι να καταστήσουμε την ΕΛΕΦΙ το μοναδικό επιστημονικό forum στο πεδίο της Φαρμακευτικής Ιατρικής, στο οποίο να συμμετέχουν τόσο οι επιστήμονες της φαρμακοβιομηχανίας, όσο και οι ερευνητές, οι επιστήμονες του ΕΣΥ, των Πανεπιστημίων και των ρυθμιστικών αρχών, οι επιστήμονες στον τομέα της Κοινωνικής Ασφάλισης κλπ. (...)

Οι σημαντικές νέες ρυθμίσεις

Η μεγάλη μας φιλοδοξία είναι να καταστήσουμε την ΕΛΕΦΙ το μοναδικό επιστημονικό forum στο πεδίο της Φαρμακευτικής Ιατρικής, στο οποίο να συμμετέχουν τόσο οι επιστήμονες της φαρμακοβιομηχανίας, όσο και οι ερευνητές, οι επιστήμονες του ΕΣΥ, των Πανεπιστημίων και των ρυθμιστικών αρχών, οι επιστήμονες στον τομέα της Κοινωνικής Ασφάλισης κλπ.

Ο συνδετικός κρίκος θα είναι η εξυπηρέτηση των σκοπών της επιστήμης της Φαρμακευτικής Ιατρικής με την ανάπτυξη της γνώσης, της εμπειρίας και των δεξιοτήτων γύρω από αυτήν με γνώμονα πάντα την αποτελεσματική και ασφαλή χρήση των φαρμάκων για την προαγωγή της δημόσιας υγείας.

Οι ρυθμίσεις που κρίθηκαν κατάλληλες για να εξυπηρετήσουν το όραμά μας, και ήδη έχουν περιληφθεί στο νέο καταστατικό, είναι εν συντομία οι ακόλουθες:

1. Διεύρυνση της βάσης:

Η Φαρμακευτική Ιατρική αποτελεί το κριτήριο εγγραφής των μελών στην ΕΛΕΦΙ. Στο αντικείμενο της Φ.Ι. συγκαταλέγονται η κλινική έρευνα, η φαρμακοεπαγρύπνηση, οι ρυθμιστικές/κανονιστικές υποθέσεις, η διασφάλιση ποιότητας, η εξασφάλιση της πρόσβασης ασθενών στις θεραπείες κλπ. Υπενθυμίζω ότι στο προηγούμενο καταστατικό τα μέλη θα έπρεπε να εργάζονται στη φαρμακευτική βιομηχανία στα ιατρικά/επιστημονικά τμήματα. Με το νέο καταστατικό, μέλη της ΕΛΕΦΙ μπορεί να είναι όλοι οι επιστήμονες που εργάζονται σε κάποιον από τους τομείς της ΦΙ ανεξάρτητα αν πρόκειται για Φ.Β. ή για κάποιον από τους φορείς του Δημοσίου, του ΕΣΥ, του Πανεπιστημίου ή των Ρυθμιστικών Αρχών και της Κοινωνικής Ασφάλισης.

2. Αίρεται ο περιορισμός του πτυχίου:

Μέλος της ΕΛΕΦΙ μπορεί να είναι κάθε επιστήμονας κάτοχος Πανεπιστημιακού τίτλου σπουδών, ανεξάρτητα από το Πτυχίο που κατέχει. Αυτό πρακτικά σημαίνει ότι όλοι οι επιστήμονες/μέλη των Ιατρικών/επιστημονικών τμημάτων της ΦΒ, καθώς και γιατροί ή άλλοι πτυχιούχοι ερευνητές, Πανεπιστημιακοί και στελέχη του Δημοσίου μπορούν να είναι μέλη στην ΕΛΕΦΙ εφόσον υπηρετούν έναν από τους τομείς της Φ.Ι. (όπως αναφέρθηκαν στην παράγραφο 1).

3. Λειτουργία Επιστημονικών ομάδων/τμημάτων Εργασίας:

Όπως προανέφερα, η φιλοδοξία μας είναι να καταστήσουμε την ΕΛΕΦ.Ι. το μοναδικό επιστημονικό forum της Φ.Ι. στη χώρα μας. Για να γίνει αυτό δυνατό, χρειαζόμαστε τη διαρκή λειτουργία επιστημονικών ομάδων που θα επεξεργάζονται θέσεις και λύσεις σε ζητήματα που μας απασχολούν στο πλαίσιο της Φ.Ι. Για την αποτελεσματικότερη εξυπηρέτηση του στόχου αυτού, το νέο καταστατικό προβλέπει τη δημιουργία ομάδων ανάλογων του τομέα της Φ.Ι. (βλέπε παράγραφο 1).

4. Έμφαση στα θέματα Δεοντολογίας και Διαφάνειας:

Για πρώτη φορά θεσμοθετείται η υποχρέωση τήρησης του Κώδικα επαγγελματικής δεοντολογίας των μελών. Δεδομένου ότι ήδη υπάρχει

ο Κώδικας Ιατρικής Δεοντολογίας (Νόμος Υπ. Αριθ. 3418, ΦΕΚ 287, 28/11/2005) καθώς και ο Κώδικας της IFAPP, στην οποία ανήκει η ΕΛΕΦΙ (ελληνική έκδοση του International Code of Ethical Conduct for Pharmaceutical Physicians), έχουμε αποφασίσει, σε σχετική συνάντηση με τα μέλη της Εταιρείας, ότι αυτοί θα είναι οι Κώδικες που μας δεσμεύουν στο πλαίσιο της ΕΛΕΦΙ. Οι κώδικες αυτοί είναι ήδη αναρτημένοι στον δικτυακό τόπο της ΕΛΕΦΙ μαζί με τον Κώδικα του ΣΦΕΕ και άλλες χρήσιμες για τα θέματα δεοντολογίας ηλεκτρονικές συνδέσεις.

Επίσης, για πρώτη φορά προβλέπεται ότι τα μέλη του Διοικητικού Συμβουλίου της ΕΛΕΦΙ δεν πρέπει να συνδέονται με οποιονδήποτε βαθμό συγγένειας και έχουν δικαίωμα εκλογής το πολύ για δύο συνεχείς θητείες.

Επίλογος

Η ανάγκη συνεννόησης σε επιστημονικά θέματα στο πλαίσιο της Φ.Ι. είναι ήδη γνωστή και συζητείται στο πλαίσιο της International Federation of Associations of Pharmaceutical Physicians στην οποία ανήκει και η ΕΛΕΦΙ (IFAPP,έτος ίδρυσης 1975) . Οι σκοποί της IFAPP είναι παρόμοιοι με τους αντίστοιχους της ΕΛΕΦΙ. Σε πρόσφατη έκδοση του περιοδικού IFAPP World (Απρίλιος 2013), υπάρχει ειδικό αφιέρωμα για την μετεξέλιξη των Επιστημονικών Εταιριών-μελών της IFAPP, ώστε να περιλαμβάνουν, όπως ήδη γίνεται σε πολλές επιστημονικές εταιρίες ορισμένων χωρών, επιστήμονες από πεδία/τομείς της Φ.Ι.

Στη χώρα μας, το Διοικητικό Συμβούλιο της ΕΛΕΦΙ με την ενεργό συμπαράσταση των μελών της, έχει διαμορφώσει τις συνθήκες για την ανάπτυξη της Φαρμακευτικής Ιατρικής, τροποποιώντας το καταστατικό και εισάγοντας θεσμούς ικανούς να εξασφαλίσουν την επιστημονική ανταλλαγή απόψεων με τελικό στόχο τη συναίνεση σε μείζονα επιστημονικά θέματα. Ελπίζουμε ότι περισσότεροι συνάδελφοι και ιδιαίτερα από τον Εθνικό Οργανισμό Φαρμάκων, τον ΕΟΠΥΥ και το Υπουργείο Υγείας θα πλαισιώσουν την ΕΛΕΦΙ, τη μοναδική στη χώρα μας επιστημονική εταιρία Φαρμακευτικής Ιατρικής.

Υπενθυμίζω ότι εγγραφές μπορούν να γίνουν και μέσω του site της ΕΛΕΦΙ (www. elefi.gr).

Είναι σημαντικό, στους δύσκολους καιρούς που βιώνουμε να αφιερώσουμε ένα μέρος του χρόνου μας με δημιουργικό τρόπο, υποστηρίζοντας τους επιστημονικούς σκοπούς της ΕΛΕΦΙ, μέσα από την ανάπτυξη της Φαρμακευτικής Ιατρικής στη χώρα μας. Η όλη προσπάθεια θα συντελέσει ουσιαστικά στη διασφάλιση της κατάλληλης χορήγησης των φαρμάκων για το καλό των ασθενών και της κοινωνίας γενικότερα.

The Randomized Registry Trial New Clinical Research Typology

Barbara Baroutsou,
MD, PhD, EMAUD, Medical Director Sanofi Greece& Cyprus

"Everything is impossible until it is done"
Nelson Mantela

Randomized clinical trials (RCTs) have generated remarkable evidence in advancing science for the benefit of the patients and public health. Randomized clinical trials especially mega-trials have transformed the practice of Medicine. However during recent years accumulating regulatory and administrative requirements made clinical trials complex, sophisticated and expensive slowing and or hindering important research.

Moreover RCTs have been criticized for delayed subjects recruitment and inadequate representativeness. What is then the value of RCTs if results are not relevant to real time and world patients' needs and clinical problems?

Conceptually could a potential solution be found to observational studies or registries given that in the past 2 decades a number of Medical Societies, Governmental Agencies, Researchers Networks and private organizations have established reputable registries where standardized patients data are gathered from different clinical settings. Investigators and public health scientists analyze registries data for defining practice patterns, outliers, safety signals and in some cases for comparative effectiveness ratios but they are confronted by validity issues owning to absence of randomization in observational findings and are consequently trapped in a methodology gap. In theory we can conduct more RCTs but in practice as they are taking long time to implement, are costly and difficult to apply and at the same time the alternative of low cost, large well designed registries with high quality data remain suspect due to the missing rigor of randomization.

Lately a new methodology appeared, the randomized registry trial and the first representative of this sort was published, namely the TASTE trial, NCT01093404 by Ole Frobert et al in New England Journal of Medicine, Oct 24 2013 ,369,1587-97.

This trial was funded by the Swedish Research Council and introduced a disruptive technology in Clinical Research. It is important to underline that the Swedish Health Care Infrastructure and their Medical Informatics are quite advanced to support selection of appropriate study population for an RCT from an existing high quality standards Registry.

More recently in December 2013 a Data Driven Trial Recruitment Program (D-TRP) in support of Sanofi and Regeneron Pharmaceuticals' PCSK9 Phase III Trial Program (ODYSSEY OUTCOMES) was announced by the alliance and in partnership with the American College of Cardiology (ACC) PINNACLE Registry in a press release by Sanofi and Regeneron.

Collaboration represents the first time the ACC's PINNACLE

Registry Research Alliance will be used for clinical trial recruitment. The American College of Cardiology has established the PINNACLE Registry Research Alliance to connect cardiovascular care teams with information about clinical trials and accelerate the systematic access of patients to potentially groundbreaking therapies. The PINNACLE Registry Research Alliance which is open to nearly 2,500 cardiovascular professionals who are part of the outpatient PINNACLE Registry will offer access to information about a range of research opportunities, expedite the identification of eligible patients and sites with the potential to benefit from participation in clinical trials and observational studies, and support the advancement of new researchers through investigator development programs.

Randomized Clinical trials are the gold standard for studying new treatments, but difficulty in identifying eligible patients is one of the main hurdles researchers face. Currently, it takes more than 10 years for a drug to come to market, and much of it is dependent on timely enrollment periods.

These novel approaches like the TASTE trial and the Pinnacle Registry (D-TRP) are bearing the promise to transform the landscape of clinical research by leveraging the usability of existing digital platforms, medical registries and e medical records to allow mega trials to happen and respond important clinical questions in reasonable time and cost.

Nevertheless these innovative options have some special interest issues to address data privacy and informed consent at the level of registries in addition to representativeness of registry data to name a few.

Clearly researchers with clinical expertise and scientific excellence, medical informatics and advanced biostatistics will reach the right balance to overcome unnecessary barriers and enable clinical research needed to advance patient care and science.

References

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3. Sanofi and Regeneron announce Collaboration with ACC Press Release December 19, 2013 http://www.sanofi.com or http://www.regeneron.com
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Risk Based Monitoring: Evolution or Trend?

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In August 2013 the FDA published a Guidance for Industry describing a risk based approach to monitoring. Specifically, "A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity. Moreover, a risk-based approach is dynamic, more readily facilitating continual improvement in trial conduct and oversight."

(Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Office of Good Clinical Practice (OGCP), Office of Regulatory Affairs (ORA), August 2013 Procedural)

It is true that clinical trials have become increasingly complicated. Continuous improvement and dynamic regulations mean more procedures, more procedural documentation and more checks to be made. The number of inspections is increasing and the findings show a trend. It is more cost effective to have a risk based approach to monitoring than engage in 100% SDV for all patients. Or is it?

The average cost of a new drug is well above one billion dollars (Matthew Herper, How Much Does Pharmaceutical Innovation Cost? A Look At 100 Companies, PHARMA & HEALTHCARE | 8/11/2013). "For sure it's not sustainable," says Susan Desmond-Hellmann, the chancellor at UCSF and former head of development at industry legend Genentech, where she led the testing of cancer drugs like Herceptin and Avastin (*Matthew Herper, The Cost Of Creating A New Drug Now $5 Billion, Pushing Big Pharma To Change, PHARMA & HEALTHCARE | 8/11/2013*). Hence, the Pharma industry had to find a new working model when it came to drug development. RBM offers such cost cutting solutions: less SDV means fewer on site visits, fewer monitoring expenses. The initial cost of setting up electronic systems for RDC, TMF etc pay off in the long run and can assist immensely in assessing risk.

Risk, however, is not a subject that can be taken lightly

when it comes to clinical research. A carefully considered risk management plan is necessary for this model to work. This involves carefully considering the risks, their severity and their likelihood. And, of course, ways to address these risks, to show sufficient oversight from the sponsor's part. Site quality inspections are likely to increase, replacing the traditional monitoring visit, even though I believe that the monitoring visit will never be completely replaced.

It is therefore likely that standard monitoring will be replaced by RBM and one cannot help but wonder:

1. Will consistently ill performing sites be eradicated from clinical research? Will sponsors never return to sites that consistently fail to meet recruitment and quality criteria? It is most probable, as the risk of carrying a poor performer or low recruiter might hamper the reputation not only of one trial, but of a whole project and even a sponsor. It is likely therefore that the bulk of clinical research will be performed at research hubs, sites geared to provide high recruitment and excellent quality.
2. Sponsors will be integrally involved in "building" sites up to success. Sponsors will have to assist research sites to become "centres of excellence" in their field, if they are interested in attracting clinical trials.
3. The cost of clinical research might decrease, but the major advantage of RBM is increasing the quality of the oversight and decreasing the quantity, achieving a better management of risk, and not so much its cost cutting capability.
4. It will be interesting to see how new clinical trial sites will be involved in clinical trials. Most sponsors will be tempted to stick to their tried and tested sites. The potential risk of a newcomer will not be easily disregarded, but sponsors should definitely try to involve these newcomers, as new sites must be available to replace older sites for research continuity.

The RBM era is at its start and there will be need for fine-tuning. Electronic systems for RDC, TMF and recruitment will improve along with risk management tools. RBM will change the way we work. We have to work smarter, invest in new technologies, support our sites and allow for the new sites to bud and bloom. It will be a collaborative effort between sponsors, CROs, Regulatory bodies and the investigators.

Pharmaceutical and Medical Devices Clinical Project Management - an Overview

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Clinical Trials have often been characterized as the most important tool for the evaluation of clinical research and its applications [1]. In a more general notion, clinical trials involving drugs or medical devices as well as post authorization studies are key activities in improving the quality of health care. Moreover, their efficient conduct and successful outcome, rely on coordinated teamwork.

Although clinical trials/studies in both pharmaceutical products and medical devices are widely recognized for their importance in improving and safeguarding health, a frequently under-stressed aspect is their management, often the critical component towards the successful conduct of the trial [2]. The management of a clinical trial can be a very complex process [3]. It materializes through specific constraints, mainly time, scope, resources and budget, requiring a multitude of abilities including: scientific skills to understand, participate in, direct and very often troubleshoot the conduct of the trial; communication skills to bring together colleagues of different expertise and roles as diverse as physicians, software engineers and marketing representatives; planning skills for the timely delivery of tasks; strategic skills to proactively design the next steps while anticipating deviations thereof; and budget skills to orchestrate the project under definite constrains. Furthermore, clinical project management requires perseverance and perspicacity; as different teams are often involved simultaneously, the level of complexity is often challenging and the particularities of each trial vital for its effective conduct.

A Clinical Trial, either in the Drug realm or in the Medical Device sector, sometimes in their intersection like combination products, means the effective and successful management of similar components. The overall strategy and design having been generated and approved, the collaboration with regulatory affairs is crucial for obtaining the necessary approvals, arranging the relative disclosures and establishing reporting procedures to competent authorities. Study sites are selected according to established guidelines. Essential documents are in both cases, drug and devices, collected and distributed to sites. Clinical operations involve site qualifications, initiation, monitoring, and close outs. Data management, programming and analysis are essential for accurate reporting through clinical study reports. Vigilance is extremely important in all cases. Good Clinical Practices apply to all operations and traceability as well as accountability are vital components of compliant studies.

Nevertheless, some of the differences in drug or device with regards to project management lie in their different mode of action. Drugs work through chemical or biological means and are usually therapeutic in their purpose whereas devices work through physical modes of action, comprising sophisticated mechanical and electrical components although often combined with biological and chemical systems, and may have diagnostic as well as therapeutic or monitoring purpose. The life cycle of drugs is much longer. Devices are invented whereas drugs are discovered. Devices are of-

ten changing during their development cycle. And while in the market, a newer improved model may already be in development, hence a shorter life cycle. While drugs undergo through multiple phases from pre-clinical development to market authorization, in devices often a single trial may be sufficient for approval, depending on their classification (part of their pre market application process) [4]. Alternatively, through equivalency (in intended scope, composition, energy source, manufacturing process and design) to a predicate device, they may even be approved without a trial.

Though the overall trial activity is frequently less in a device clinical trial, team and Investigator training, which may often involve technically (and extensive use of software) oriented tasks, can be more demanding during device clinical trials, thus requiring extensive planning, practice and preparation. Also, team meetings may also be more technical in nature since the Investigator's technique is often vital to the continuation of the trial and to the assessment of the device. Ease of use is of tremendous importance even for a very advanced device, thus the unique characteristic of IFU (Instructions for use) as opposed to package insert in addition to the Investigator Brochure. Mainly due to the design purposes of devices, methodological differences in the conduct of the trial are also apparent as it is often difficult to 'blind' (for assessment purposes 'blind' evaluators instead of 'blind' investigators are used) or randomize (i.e. implantable devices). Other differences include safety reporting and vigilance particularities, as well as the sample size involved.

Drug or Medical Device Trials are conducted under different regulatory guidelines and pathways. Nonetheless, regulatory clearances in devices may be more flexible. Pharmaceutical clinical trials follow different phases (traditionally called I, II and III), which may last for years and are often followed by post authorization studies (phase IV) necessary for surveillance and monitoring of common practice. Examples of regulations and guidelines are the European Medicines for Human Use Regulations [5], the European Directives for clinical trials 2001/20/EC and 2005/28/EC [6]. In Greece the EC directives are applied through Ministry Decisions ΔΥΓ3/89292 (FEK B1973/31-12-2003) and ΔΥΓΑ/9602 (FEK B24/25-01-2007) respectively. In addition, the National Organization for Medicines, EOF, has issued several guidelines for their implementation [16]. Other applicable guidelines include the European Medical Authority's GVP [7], the ICH Guidelines (E3, E6 and E9) [8] and the guidelines of the different FDA departments in the United States (CDER for drugs and CBER for Biologics) [9]. On the other hand, medical devices are governed by directives such as the Medical Device Directive 93/42/EEC as amended by directive 2007/47/EC [10], the Active Implantable Medical Device Directive 90/385/EEC as amended by directive 2007/47/EC [11], and the In Vitro Diagnostic Directive (98/79/EC)[12]. In the States the respective FDA offices are the CDRH [13] for devices, the OCP for combination products [14] and the OIVD for In Vitro Products [15]. Greece has adapting the EC directives issuing two Common Ministry Decisions, ΔΥ8δ/Γ.Π. οικ 130648 (FEK B' 2198/2-10-2009, 'about Medical Devices', and ΔΥ8δ/Γ.Π. οικ 130644 (FEK B' 2197/2-10-2009, 'about Active Implantable Medical Devices' as well as the EOF decision, ΔΣ/ΕΟΦ 6209/2009 (FEK 199B'/06.02.2009), 'Good Manufacturing Practices specifications for medical devices' [17].

Finally, a trial, either of an investigational drug or device or even of a post authorization study, may be conducted in one country or be international. In all cases, regulatory differences have to be considered as well as local and international regulations.

All considered though, a systematic and thorough approach, always through the prism of pro-activeness, team collaboration, compliance and awareness of updated guidelines, will work marvelously towards a very rewarding experience and sense of contribution.

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AGEING

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Ageing (aging) or senescence is the complex developmental process of accumulative changes to molecular and cellular structures that disrupt metabolism and result in progressive deterioration of physiological function, loss of viability, increase in vulnerability and death [1].

Senescence occurs both on the level of individual cells (cellular senescence) as well as on the level of the whole organism (organismal senescence)[2,3].

Ageing is characterized by the declining ability to respond to stress, increased homeostatic imbalance, and increased risk of ageing-associated diseases such as cancer and cardiovascular disease. Senescence indirectly is the leading cause of death, where there is always a specific proximal cause.

Regardless the ending, senescence rate is not universal. Numerous species show negligible senescence and exhibit very long lifespans, such as trees, invertebrates and fish [4].

In contrast, accelerated ageing and ageing related changes emerge in humans in extremely rare genetic diseases, called progeroid syndromes. Sufferers exhibit symptoms resembling accelerated ageing and have reduced lifespan. Accelerated ageing diseases arise from genetic mutations causing defects either in the lamin A/C protein involved in the stability of nucleus (e.g. Hutchinson-Gilford progeria, Bloom syndromes) or in DNA repair proteins (e.g. Werner, Cockayne, xeroderma pigmentosum syndromes) [5].

The exact etiology of senescence is still not clear. The process of senescence may originate from a variety of different mechanisms and exist for a variety of different reasons.

Cellular and organismal senescence

Cellular senescence is the phenomenon where isolated normal cells demonstrate a limited ability to divide in culture. Normally, after about 50 divisions through the process of cellular mitosis, cells become post-mitotic i.e. they can no longer replicate experiencing replicative senescence (Hayflick phenomenon) [6].

Organismal senescence is the ageing of whole organisms. Among species differences exist in maximum life span, corresponding to changes in a variety of physiological processes.

Cellular replicative senescence is causally implicated in generating age-related phenotypes in organisms. Removal of senescent cells can prevent tissue dysfunction and extend healthspan — the period of life spent in relatively good health. Pharmaceutical eradication of senescent cells in mice leads to greater resistance against ageing-associated diseases (cataracts, muscle wasting, skin wrinkling) and increased exercise potential [7]. In mammals, a decline in stem-cell

function is likely to be an important cause of age-related pathology [8]. Not all cells in organisms become senescent, the germline cell lineage (traced from fertilized egg to fertilized egg) is immortal.

On the other hand, apoptotic cells self-destruct experiencing a programmed cell death. This cellular suicide may benefit the organism as a whole. For example, the differentiation of digits (fingers and toes) in a developing human embryo occurs because cells between the digits apoptose.

In those species where certain cells become post-mitotic, it is suggested that cellular senescence evolved as a way to prevent the onset and spread of cancer (as long as cell division continues somatic cells accumulate DNA mutations and risk of becoming cancerous).

Evolutionary concept of ageing

Evolution is the unifying basis of biology and may explain ageing involving the role of natural selection and its stronger effect upon the young rather than the old.

The evolutionary concept of ageing encompasses the importance of two parameters: reproduction resources and extrinsic mortality.

On one hand, ageing is the result of life investing resources in reproduction rather than in maintenance of the body (disposable soma theory) [9].

Any genetic, developmental or physiological effect that increases the reproductive performance of the young will evolve despite the costs that may impose on the old. That is, traits benefiting early survival and reproduction will be selected even if they contribute to a decreased lifespan. (..)

Any genetic, developmental or physiological effect that increases the reproductive performance of the young will evolve despite the costs that may impose on the old. That is, traits benefiting early survival and reproduction will be selected even if they contribute to a decreased lifespan [10]. For example in humans, some of the genetic variants that increase fertility in the young are now known to increase cancer risk in the old. Such genes include p53 [11] and BRCA1 [12].

In these terms, the antagonistic pleiotropy evolutionary theory of ageing is formed [13]. A single gene may affect multiple traits. Some traits that increase fitness early in life may also have negative effects later in life, but because many more individuals are alive at young ages, even small early positive effects can be strongly selected for, whereas even large later negative effects may be ignored and not be depleted.

Moreover, natural selection can tolerate lethal and harmful gene variants, if their expression occurs after reproduction period. Senescence may be the product of such action [14].

On the other hand, ageing is believed to have evolved due to the increasingly smaller probability of an organism to be alive at older age, due to predation, accidents and disease (extrinsic mortality). As a result, if disastrous genetic mutations are effectuous late in life, their consequences may be completely indifferent to selection [15].

Young cohorts, not yet depleted by extrinsic mortality, contribute far more to the next generation than the few remaining older cohorts. The force of selection is very weak against late-acting deleterious mutations that affect only the few older individuals, and therefore these mutations may spread into the population over evolutionary time.

As example, the mutation which causes fatal neurological Huntington's disease onseting at age 45 may have not been eliminated by natu-

ral selection, since in human prehistory few individuals survived until age 45. The force of selection against such late-acting deleterious mutation was small.

A prediction made by this model is that species that have high extrinsic mortality in nature will age more quickly and have shorter intrinsic lifespans. High extrinsic mortality will not let selection against late-acting deleterious mutations and thus will lead to accelerating ageing due to these mutations and a shorter lifespan. Indeed, there is a correlation among mammals between body size and lifespan, meaning more predators for the low sized. Another example is that bats and birds have similar size as rodents, but live much longer, as they have fewer predators. Seabirds, having the fewest predators of all birds, live longest.

Another angle of viewing ageing evolution is through group selection. As ageing is manifestly deleterious to the individual organism, it may not be a product of natural selection on the level of single organisms. Group population selection may explain ageing puting forward the notion that those groups consisting of earlier ageing individuals may excibit better group survival. The increase in individual mortality rate could prevent a population from depleting their food resources and thereby increasing the probability for group survival [16].

Non-biological theories of ageing

Ageing can be explained on a non-biological basis. In reliability theory that follows a general concept about systems, ageing is seen as an inherent consequence of systems. Ageing may be manifested in systems redundant in irreplaceable elements which do not age per se but undergo an advancing failure probability rate in proportion to time.

Biological theories of ageing

Numerous biological theories have been proposed to explain ageing. These theories may interact with each other. They are divided in two main categories: stochastic - error theories which explain ageing process as the accumulation of errors and genetic - programmed theories which see ageing as the result of changes in gene expression.

Stochastic theories consist of impacts inflicted on cellular components, structural proteins or DNA by free oxygen radicals and sugars leading to damage or cross-linking. These theories suggest that ageing is a form of disease.

Genetic theories propose the operation of genetic “biological clocks” which affect body functions such as maintenance, repair and defense.

Stochastic – error theories

Wear and tear

Wear and tear is a general idea according to which ageing associated changes are the result of chance damages occuring due to continued use and accumulating over time on cells and organs [17].

General imbalance

General imbalance theories of ageing suggest that body systems, such as

the endocrine, nervous, and immune, gradually decline and ultimately fail to function. The rate of failure varies in different systems [17].

The Reproductive hormones theory suggests that ageing is caused by changes in hormone signaling occuring over lifespan. Reproductive hormones acting in an antagonistic pleiotropic manner, promote growth and development early in life to secure species reproduction, but become deregulated and drive senescence later in life [18].

Similarly, ageing may be seen as a progressive failure of genes involved in homeodynamics (homeostasis) due to stochastic events leading to molecular damage and molecular heterogeneity.

Accumulation theories

Accumulation theories suggest that ageing is due to accumulation of chemical deffects inflicted by agents either of environmental or of regular cell metabolism origin. There is a buildup of damaged products ultimatly interfering with cell functions (accumulative waste theory) [17].

One of the earliest ageing theories states that fast basal metabolic rate corresponds to short maximum life span. In general, this theory does not adequately explain the differences in species lifespan. However, there may be some validity to the idea that a fast metabolism may reduce lifespan as a result of accumulation of metabolic by-products and damages.

Chemical damage to structural proteins can lead to loss of function. For example, damage to structural collagen of blood vessel walls can lead to hypertension and atherosclerosis. Similarly, damage to enzymes may reduce cellular functionality.

The cross-linkage theory proposes that ageing results from accumulation of cross-linked compounds that interfere with normal cell function [19][20]. Chemical damage inflicted by metabolic oxygen and sugars impacts structural proteins or DNA causing breakage of biopolymer chains, attachment of chemical groups and cross-linking.

Glycation is a process where sugars such as glucose and fructose can react with amino acids such as lysine and arginine or DNA bases such as guanine and lead to cross-linking of biomolecules. Thereby, diabetes patients develop senescence-associated disorders much earlier than the general population, but such disorders can be delayed by controling blood sugar. There is evidence that sugar damage is linked to oxidant damage in a process termed glycoxidation.

Misrepair- accumulation theory suggests that ageing is the result of the accumulation of “misrepair” i.e. of defects in cell structures after incorrect function of repair mechanisms [19].

Free radical error accumulation theory - Reactive oxygen species

According to this theory, free radicals (unstable and highly reactive byproducts of regular cell metabolism) interact with cellular components causing irreversible damage [21]. In mitochondria under normal aerobic conditions, a part of oxygen is converted to reactive compounds (reactive oxygen species such as superoxide, peroxides, hydroxyl radicals and singlet oxygen) which in turn can generate free

radicals capable of damaging structural proteins and DNA.

Oxidative damages accumulate with age, but it is not definite whether the free-radicals or the ageing is the primary cause. However, symptoms of ageing may be generated by oxygen-containing radicals which create oxidative stress damages [22,23]. There is a positive feedback between damaged proteins and acceleration of ageing process [24].

There exist genes conferring protection against free oxygen radicals and oxidative stress in mitochondria, thereby slowing ageing process. For example, superoxide dismutase gene can extend yeast lifespan when overexpressed. Also, the introduction of catalase gene results in a 20% lifespan increase and improved performance in transgenic mice[25].

Autophagy

Autophagy performed through the actions of lysosomes is a major process for cells to recycle old or damaged parts such as protein aggregates and degenerate mitochondria, thereby allowing efficient functioning [26].

Autophagy declines with ageing and accumulation of damage contributes to age-related cellular dysfunction. Aberrant regulation of autophagy has been linked to several ageing related diseases, including cancer, diabetes, cardiovascular and neurodegenerative diseases [27].

Autophagy may increase longevity by recycling damaged parts as those produced by reactive oxygen radicals. Autophagy is increased in periods of starvation [28].

Somatic mutation theory is a biological theory proposing that ageing results from damage to DNA. Since DNA is the formative basis of cell structure and function, damage to it can lead to loss of functionality and cell death. (...)

DNA damage theory

Somatic mutation theory is a biological theory proposing that ageing results from damage to DNA. Since DNA is the formative basis of cell structure and function, damage to it can lead to loss of functionality and cell death. The integrity of the genome is safeguarded by the cellular checkpoint pathways and machineries of repair that counteract DNA damage.

DNA damage is implicated in cancer, apoptosis and ageing. DNA damage especially due to reactive oxygen species has been proposed as the cause of ageing and ageing related disorders [19-23,29].

As explained below, DNA damage cause of ageing may be mediated by alterations in Lamin A/C gene, defects in DNA repair mechanism or damage in RecQ DNA helicases.

Lamin A/C - Hutchinson Gilford progeria

Proteins in the lamin family of are involved in nuclear stability, chromatin structure and gene expression and replication. Lamin A/C is a protein encoded in humans by the LMNA gene [30,31].

Lamin is required to ensure the nucleus shape, as it acts like a scaffold protein for the formation of a filamentous meshwork underlying the inner nuclear membrane. Once the protein has undergone this role, a farnesyl group is removed from and it is released from the nuclear membrane. Failure of this farnesyl group removal, permanently affixes the protein to the nuclear membrane and causes a characteristic

nuclear blebbing [32]. In addition, mutations in LMNA gene lead to mislocalisation of chromatin and misregulation of gene expression, limiting the ability of the cell to divide [33,34].

Hutchinson–Gilford progeria is a syndrome characterized by premature and accelerated ageing (~7 times the normal rate) whereby patients die by the age of 13 from atherosclerosis complications such as heart attack or stroke [35,37]. This syndrome is caused by sporadic somatic mutations in the LMNA gene which lead to failure of the removal of farnesyl group from lamin A/C, the mutated proteins called progerins. These mutations are not inherited but are developed during cell division in gametes or zygote [38,39].

In nematodes, comparable lamin changes occur in somatic cells progressively over lifespan [40]. The mutated form of lamin A may play a role also in normal human ageing, given that its production is activated in wildtype senescent cells [34].

Defects in DNA repair

Many DNA repair affecting genes influence life span and the process of ageing. The majority of accelerated ageing diseases are due to defective DNA repair enzymes. Genetic mutations which lead to defects in the cellular machinery repairing DNA, are one of the main causes of progeroid syndromes.

As explained below, mutations in two classes of DNA repair proteins have been associated with progeroid syndromes. The RecQ protein-like helicases (RECQLs) are connected to Werner syndrome and Bloom syndrome, while the nucleotide excision repair proteins (NER) are linked to Cockayne syndrome and Xeroderma pigmentosum.

RecQ-associated progeroid syndromes

RecQ is a family of DNA helicases that bind and temporarily unwind double-stranded DNA in order to fascilitate genome replication during mitosis. These enzymes are also required to repair damaged DNA and to prevent abnormal DNA recombination [41].

Defects in DNA helicases are linked to an increased predisposition to cancer and ageing phenotypes[42]. There are five genes encoding RecQ in humans and defects in RECQ2 and RECQ3 lead to Werner and Bloom syndrome, respectively [32,41].

Patients of RecQ-associated progeroid syndromes show an increased risk of developing cancer caused by genomic instability and increased mutation rates. On the cellular level, cells of affected individuals exhibit chromosomal abnormalities, genomic instability, and sensitivity to mutagens [43].

Werner's syndrome patients exhibit growth retardation and premature ageing [44,45]. Mortality is mainly due to cardiovascular disease or cancer [5,46]. Mutated RECQL2 leads to a reduction in DNA repair [47]. Furthermore, the aberrant helicase2 negatively affects the function of tumor suppressor protein p53, leading to a reduction of apoptosis and increased survival of Werner's syndrome cells in the body [48]. Cells from affected individuals excibit a reduced lifespan in culture [49].

Bloom's syndrome caused by mutations in the RecQ3 helicase gene is presented with retardation of growth, premature ageing and increased

risk of cancer [50]. Apart from normal helicase activity, homologous recombination (where two copies of DNA in close physical proximity cross-exchange genetic information during genome replication) is also affected. The later is due to helicase3 interaction with topoisomerase IIIα and RMI2 [39,51,52]. Homologous recombination goes off unsuppressed, leading to higher rates of mutation (~10-100 times above normal) with introduction of gaps and breaks and disruption of the function of genes [36,53].

Nucleotide excision repair NER associated progeroid syndromes

Nucleotide excision repair (NER) is a DNA repair mechanism. In NER, a damaged segment of a DNA strand is removed. Defects in genes controlling the NER pathway have been linked to progeroid syndromes such as Cockayne syndrome and Xeroderma pigmentosum [54-56].

In Cockayne's syndrome the mean life expectancy is 12 years [57]. Mutations in the cross-complementing genes ERCC8 ERCC6 cause alternate splicing of pre-mRNA leading to production of abnormal CSA CSB proteinsand to RNA polymerase II ubiquitination and degradation[58,59]. As a consequence, DNA is no longer repaired through the transcription-coupled nucleotide excision repair mechanism (TC-NER), and the accumulation of mutations leads to cell death [57].

Xeroderma pigmentosum is caused by mutations in genes involved in the DNA nucleotide excision repair pathway, for example in the gene coding a DNA polymerase that prevents UV-dependent DNA damage[55].

Genetic – programmed theories

Genetic theories propose that ageing is programmed within genome. Ageing is interpreted as a process of regulation of gene expression bringing about ageing associated alterations and decrease in lifespans. The regulatory program can be influenced by environmental factors and even intervened and partially overturned.

The first gene mutation found to increase longevity was the age-1 gene in the worm Caenorhabditis elegans, encoding the catalytic subunit of phosphatidylinositol 3-kinase (PI3K) an intracellular signal transducer enzyme[60]. Different mutations to C. elegans found to increase lifespan by 2 or even up to 10 times normal [61,62]. Genetic mutations can increase maximum lifespan also in higher organisms, for example an altered gene in mice by 1.5 times normal [63]. In general, mutations that slow ageing also postpone age-related disease. There have been identified over 800 genes extending lifespan in model organisms: 454 in the nematode worm (Caenorhabditis e.), 236 in the bakers' yeast (Saccharomyces c.), 79 in the fruit fly (Drosophila m.) and 68 in the mouse (Mus m.)[64].

Telomeres

Telomeres are structures at the ends of chromosomes which have been shown to shorten with each successive cell division. Shortened telomeres activate a mechanism that prevents further cell replication[65].

Telomerase is a reverse transcriptase enzyme which functions in

the opposite way and elongates telomeres. In about 85% of tumors, the evasion of cellular senescence by cancer cells is the result of up-activation of their telomerase genes [17].

Telomere shortening brings about extensive alterations in alternative RNA splicing and produces proteins called progerins, such as the mutated lamin A/C, leading to cellular senescence[66]. Also, inhibition of replication is imposed on tissues such as bone marrow and arterial endothelium where cell division is needed constantly throughout life[67]. Nevertheless, telomerase concentrations and telomere length have not shown to correlate with length of lifespan in animal models[68,69].

Genetically altered mice, engineered not to produce telomerase naturally, were rejuvenated after chemical induction of telomerase. Organs such as pleen, liver, intestines, testes and brain recuperated from degenerated state. Moreover, mice genetically engineered to produce 10 times the normal level of telomerase, lived 26% longer than normal [65].

Epigenetic changes are heritable changes in gene activity which are not caused by alteration in the DNA sequence. The most known epigenetic process is methylation in which methyl groups are attached to the DNA affecting gene expression through transcription. (..)

Epigenetics

Epigenetic changes are heritable changes in gene activity which are not caused by alteration in the DNA sequence. The most known epigenetic process is methylation in which methyl groups are attached to the DNA affecting gene expression through transcription. This process of demethylation/remethylation is referred also as reprogramming[70] and materializes during germ cell development, zygote formation, carcinogenesis [71,72] and ageing [73].

DNA methylation in human tissues increases proportionally to ageing. A biological clock acts within the genome accompanying ageing stages of the organism and of each separate organ. This correlation reveals a heritable measure of age acceleration but the causality has not been explained yet. DNA methylation level also correlates with the number of cell divisions of cultured cells [73].

Following this finding, an age predictor test is developed using saliva samples to determine DNA methylation levels. This test with no further information can predict the age of human subjects with an accuracy of five years [74].

DNA methylation was analyzed in thousands of healthy or tumor cell samples. It emerged that methylation is carried out more rapidly until the age of 20 and then decelerates. Also, some body tissues and organs appear younger or older (the difference could reach even 10 years) in comparison to their neighboring counterparts or to the chronological age of the donor.

Cancerous tissues are comparable to ageing tissues as they appear on average 36 years older than healthy tissue. DNA methylation age is close to zero for embryonic stem cells. Induced pluripotent stem cells (adult stem cells reprogrammed to a semi embryonic state) also have a DNA methylation age of zero.

RAS genes

RAS is a GTPase family of proteins controlling intracellular signaling in processes such as cytoskeletal integrity, proliferation, differentiation,

cell adhesion, cell migration and apoptosis. Ras proteins activate several pathways downstream resulting in stimulation of genes involved in cell growth and division.

Ras proteins are often deregulated in cancers, leading to decreased apoptosis and increased invasion and metastasis.

RAS genes are known to affect the ageing process, for example their overexpression in yeast increases lifespan by 30% [75].

SIRT genes

Sirtuin proteins are a class of proteins implicated in a wide range of cellular processes such as gene activation, mitochondrial biogenesis, stress resistance, apoptosis and ageing. The sirtuin genes have a significant effect on the lifespan of yeast and nematodes [76-80].

The Sir2 gene in yeast is responsible for cellular regulation and is upregulated improving energy efficiency under caloric restriction[81].

The mammalian sirtuin SIRT1 gene assists in the repair of DNA and suppresses age-dependent transcriptional changes [82]. Male transgenic mice overexpressing SIRT6, showed an increased lifespan of about 15%, attributed to lower serum levels of insulin-like growth factor 1 (IGF1) and changes in its signaling pathway [83,84].

Mammalian SIRT1 deacetylate FOXO proteins in response to oxidative stress19, which, in turn, shifts their target specificity towards genes involved in stress resistance [85].

Caloric restriction

Many mutations that extend lifespan affect genes that respond to stress or nutrient stimuli. When food is plentiful and stress levels are low, these genes support growth and reproduction. Under harsh conditions, their activities change in order for the animal to undergo a physiological shift towards cell protection and maintenance. This shift not only protects the animal from environmental stresses but also extends lifespan. The best known signal to which animals respond in such way is dietary restriction [85].

Reduction in calorie intake (dietary restriction) in the absence of malnutrition, is currently the only known intervention to extend lifespan in many different species including yeast, worms, flies and mice[86]. Restricting calories to 30–50% less than ad libitum, has been shown to increase lifespan in mice and Rhesus monkeys [87,88]. Sirtuin proteins are implicated in the extention of lifespan in flies and mice by dietary restriction [85].

Dietary restriction not only extends lifespan but also delays the incidence of age-related decline and disease, for example, cancer, cardiovascular disease, diabetes, cognitive decline and neurodegeneration in mammals [86,89]. Caloric restriction may have protective effect against secondary ageing pathologies such as the risk of Type 2 diabetes and atherosclerosis in man [90].

As will be described below, reduced IGF-1 signaling may contribute to the anti-ageing effects of caloric restriction [91]. Among a number of other factors, nutrition acts as a stimulant while fasting acts as an inhibitor in growth hormone (GH) and insulin-like growth factor

1 (IGF-1) levels. A cascade of effects may be portrayed from caloric restriction to IGF-1-like inhibition to mTOR pathway inhibition continuing to mitochondrial function and oxidative stress avoidance and finally to increase in autophagy.

Insulin / IGF-1 signaling

The first pathway shown to influence ageing in animals was the insulin/IGF-1 pathway [92]. Insulin-like growth factor 1 (IGF-1) is a hormone similar in molecular structure to insulin, produced in the liver aftrer stimulation by growth hormone (GH). IGF-1 is a potent inhibitor of apoptosis and like insulin, it plays an important role in activation of cell growth and proliferation through its receptor binding.

Mutations that reduce insulin/IGF-1 signaling have been shown to decelerate ageing and extend lifespan in a wide range of organisms, including nematodes, fruitflies and mice [85,86] and possibly humans[93-96]. Furthermore, mouse models lacking the GH receptor gene and deficient in IGF-1 live longer and present a delay in age-related changes compared to normal controls[97].

Inhibiting insulin/IGF-1 signalling increases lifespan through downstream changes in expression of various stress-response genes mediated by transcription factors[85]. Dietary restriction leads to reduced insulin/IGF-1 and mTOR signaling in both invertebrate and mammalian aging model organisms[98]. Activation of the tumor suppressor gene PTEN also leads to inhibition of this pathway and causes insensitivity of cancer tumors to insulin and IGF1. PTEN is also activated in caloric restriction[99,100].

The Laron syndrome, is characterized by an insensitivity to GH, caused by mutations in the GH receptor gene. Patients present with exceptionally low levels of IGF-1 and its carrier protein. The principal feature of Laron syndrome is extremely short stature (dwarfism) [101]. Effective treatment relies in biosynthetic IGF-1 administration before puberty. Laron syndrome patients have strikingly low rates of cancer and diabetes and are somewhat protected against ageing[102]. It is theorised that GH receptor gene mutation and reduction of IGF-1 signaling may imply a key to life extension[103].

The mTOR pathway

An overwhelming amount of data has established the mTOR signaling pathway as a central evolutionarily conserved process into which ageing causes and effects of either stochastic or genetic nature are intercalated.

The evolutionarily conserved mechanistic (or mammalian) target of rapamycin (mTOR) gene belongs to the gene family of PI3K kinase phosphorylating enzymes (protein kinases) involved in major cellular functions such as cell growth, proliferation and differentiation[104-106]. The gene partipates to the PI3K/AKT/mTOR intracellular signalling pathway[104] and generates two different protein complexes (mTORC1 and mTORC2). Activation of the mTOR pathway initiates a downstream phosphorylation cascade leading to promotion of mRNA translation and activation of ribosome function[107]. As a consequence, protein and lipid biosynthesis is stimulated whereas protein breakdown is inhibited.

The mTOR pathway acts as a master regulator of cellular growth and of metabolic functions related to apoptosis, cancer and longevity[108]. The mTOR pathway is dysregulated in human diseases such as diabetes, obesity, depression. In certain cancers (e.g. breast, small cell lung) the pathway is overactive leading to reduced apoptosis and increased cell proliferation[107].

The mTOR pathway is activated by hormonal and nutrient stimuli. Positive inputs from upstream pathways include insulin and other growth factors such as insulin like growth factors IGF-1 and IGF-2, nutrients such as amino acids, oxygen and increase in cellular energy levels[109,110].

Inhibition of TOR activity has been found to extend lifespan in yeast, worm, fruit fly and mouse species[111-114]. Inhibition of mTORC1 was found to reduce progerin effects in Hutchinson–Gilford progeria syndrome cells[115].

Inhibition of mTORC1 also brings about positive effects on numerous age-related pathologies in model organisms and humans such as cancer, autoimmune, Parkinson's, dementia, cardiac, cerebral ischaemia, metabolic or retinopathy[116-119].

The picture of mechanisms by which inhibition of mTORC1 enhances longevity or improves age-related pathologies is complex. Multiple mTORC1 regulated processes seem to contribute to the pro-longevity effects of mTOR inhibition in an overlapping manner. The relationships between mTORC1 and insulin / IGF-1 signaling reflect this complexity. mTORC1 may modulate ageing by mechanisms that overlap insulin/ IGF-1 signaling.

There is a consensus that dietary restriction contributes to longevity and health benefits as a result of mTORC1 inhibition. Dietary restriction acts upstream on mTORC1 and results in reduction of mTORC1 activity partly through activation of AMP-activated protein kinase (AMPK). (...)

There is a consensus that dietary restriction contributes to longevity and health benefits as a result of mTORC1 inhibition[85]. Dietary restriction acts upstream on mTORC1 and results in reduction of mTORC1 activity partly through activation of AMP-activated protein kinase (AMPK). This enzyme is a key sensor of low cellular energy status and is activated in response to low ATP levels[120]. One of its effects is inhibition of mTORC1. Overexpression of AMPK is sufficient to extend lifespan in the worm C. elegans[121,122]. Dietary restriction additionally acts as an inhibitor of GH and IGF-1 levels, thus its anti-ageing effects may be mediated by reduced IGF-1 signaling through PI3K/AKT/mTOR pathwayIn both invertebrate and mammalian aging model organisms, dietary restriction leads to increased AMP kinase activity and reduced insulin/IGF-1 and mTOR signaling[85].

The lifespan extension by mTOR repression is possibly mediated by the downstream regulation of transcription factors of FOXO gene family. FOXO proteins function as a trigger for apoptosis through upregulation of genes necessary for cell death and downregulation of anti-apoptotic proteins[123,124]. Inhibition of FOXO transcription factors by phosphorylation by proteins such as Akt in the PI3K/AKT/ mTOR signaling pathway promotes cell survival[125,126]. Moreover, FOXO3 is involved in protection from oxidative stress by upregulating antioxidant proteins such as catalase. In response to oxidative stress mammalian SIRT1 deacetylates FOXO proteins and leads to expression of genes involved in stress resistanceFOXO3 polymorphisms are associated with longevity in humans[85].

Prolongation of lifespan by mTORC1 inhibition may also be attributed

to regulation of mitochondrial functions[127-129] and of Oxidative Capacity through Stress Responses[130,131].

mTORC1 has a central role in stem-cell function decline and mTORC1 inhibition can preserve stem-cells from losing their potency in organs such as haematopoietic and intestine[132,133].

Inflammation may play a role in ageing as it is associated with several age-related disorders in mammals[134]. IFNγ, is a cytokine associated with a number of autoinflammatory diseases[135]. Human skin fibroblast cells in culture are shown to lose their juvenile characteristics as an effect of ageing and the impact of IFN-gamma[2,3]. The mTOR is often associated with inflammation and a reduction in chronic age-associated inflammation by mTORC1 inhibition could be a mechanism by which longevity and age-related pathologies might be improved[136-138].

Activation of autophagy by mTORC1 inhibition is a process that probably has a central role in promoting longevity. Inhibition of mTORC1 mediated by dietary restriction or rapamycin, promotes removal of damaged and dysfunctional cellular components through induction of autophagy and results in lifespan extension[139-141].

In conclusion, longevity may be connected to caloric restriction and lower insulin/IGF-1 signaling leading to inhibition of the mTOR pathway. Consequently, increased autophagy may reduce the effects from reactive oxygen species by improving the cleaning of cells and recycling damaged protein and DNA macromolecules and cellular particles. Further damage may be reduced, cells may continue full functional and thereby longevity may increase[142].

Anti-ageing approaches

Maximum lifespan of a species is determined by the rate of ageing inherent in its genes and by environmental factors. Average lifespan in a population is lowered by infant and child mortality frequently linked to infectious diseases or nutrition problems. Extension of expected lifespan can be achieved by access to improved medical care, vaccinations, good diet, exercise and avoidance of hazards such as smoking.

From a public-health perspective, it would be preferable to compress morbidity from most of lifetime's illnesses as close to the end of life as possible[143]. Slowing ageing should increase both lifespan and healthspan free from chronic disease or disability.

The global anti-ageing product market (nutrition, physical fitness, skin care, hormone replacements, vitamins, supplements) reaches about $100 billion per year. However, only few of the existing remedies have been systematically tested for longevity effects. Some molecules are shown to retard or reverse the biological effects of ageing in animal models. Minerals such as selenium and zinc have been reported to extend the lifespan in rodents, though in addition to significant toxic effects[144-146]. Antioxidant supplements, such as Vitamin C, Vitamin E, Q10, lipoic acid, carnosine and N-acetylcysteine, might reduce toxic oxidative effects, nevertheless, trials suggested that some of them might cause harm[147]. Traditional herbs, including a Chinese tea and Indian rasayanas used for health-span extention showed positive results in animal models[148,149]. Polyphenol antioxidants

present in coffee, red wine and tea have been associated to counteract the oxidative stress process[150,151]. The plant polyphenolic compound resveratrol, an ingredient of red wines, is a SIRT1 stimulant showed to extend lifespan in short-lived organisms and to inhibit age-related deterioration in mice[152-154].

Medicines that lower the IGF-1 level are on the market prescribed for the treatment of acromegaly disease caused by excessive GH production[103].

Drugs that target the mTOR pathway could be used to slow ageing and reduce age-related pathologies. Pharmacological inhibition of this pathway is sufficient to extend lifespan in both invertebrates and mice [98]. Inhibitors of mTOR pathway are already clinically approved for immune suppression, such as rapamycin[155]. Rapamycin was found to extend the life lifespan of yeast[156], worms[157], fruitflies[158] and of mammals (mice) by up to 38%[159-161]. Additionally, many age-related diseases can be delayed by rapamycin[161-163]. However, immunosuppressive action and other undesirable effects of rapamycin could not be tolerated in an anti-ageing setting[155,163,164].

A variety of strategies may serve the purpose of ageing inhibition in the future. Ageing viewed as a disease, may stimulate pharmaceutical companies to develop life extension therapies. Many experts in the biology of ageing believe that pharmacological interventions to slow ageing will certainly evolve[85]. Other future interventions may include nanomedicine techniques to countrer ageing processes, stem cell and cloning therapies for cell and body parts replacement, combination of biochemical and genetic techniques, genetic modifications by gene therapy to increase DNA repair, reduce oxidative damage or reduce cell apoptosis, or prevention of onset of ageing genes[165-167].

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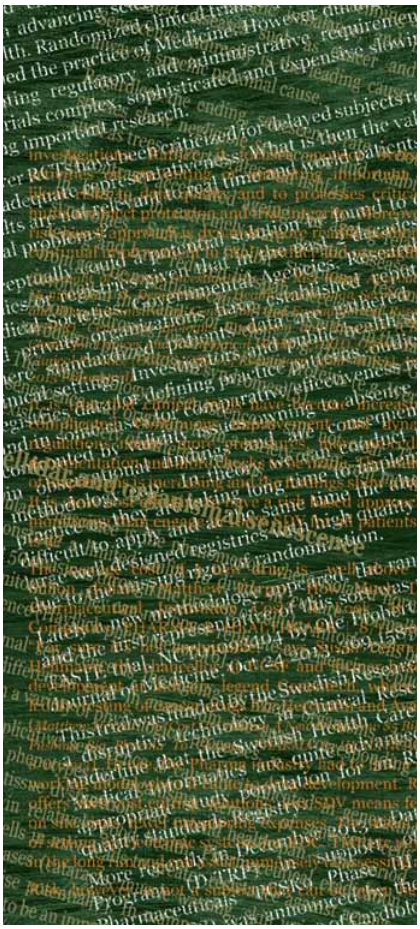

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