

PROJECT REPORT

COMPARISON OF BLOOD SERVICES AND CLINICAL TRANSFUSION PRACTICES IN ZIMBABWE AND THE NETHERLANDS: what are the Key Lessons?

Mapako T^{1,2}, Janssen MP³, Van Den Burg P⁴, Smid M⁴, Mvere DA², Emmanuel JC², Postma MJ¹, Rusakaniko S⁵, Groningen HB⁶, Van Hulst M^{1,6}

1. *Unit of PharmacoEpidemiology & PharmacoEconomics (PE2), Department of Pharmacy, University of Groningen, Groningen, The Netherlands*
2. *National Blood Service Zimbabwe, Harare, Zimbabwe*
3. *Julius Center for Health Sciences and Primary Care, MTA Department, University Medical Centre Utrecht, Utrecht, The Netherlands*
4. *Sanquin Blood Supply, Amsterdam, The Netherlands*
5. *Department of Community Medicine, College of Health Sciences, University of Zimbabwe, Zimbabwe*
6. *Martini Hospital, Groningen, The Netherlands*

ABSTRACT

INTRODUCTION

Tracking blood safety status of member states by World Health Organisation is now a routine activity through Global Database for Blood Safety. To understand further the differences between high income and low-income countries a detailed review may be warranted. In this review, the blood services of Netherlands and Zimbabwe were compared.

METHODOLOGY

A study visit to Netherlands was undertaken and the key findings from this visit were compared with equivalent data from Zimbabwe. Key thematic points were summarised from the review of the reports as well as the outcomes from key observations and informant discussions. Lessons learnt and recommendations were drawn for each thematic area considered.

KEY FINDINGS

The difference in geographical land sizes (Zimbabwe 10 times larger) and population demographics (Zimbabwe predominately youths) poses different challenges to Netherlands and Zimbabwe. The organisation and management structures of the Services are similar and both rely on 100% voluntary non-remunerated blood donors. Despite the high transfusion transmission infections (TTI) rates in the general population in Zimbabwe the testing technology is low as compared to Netherlands. However, Zimbabwe through other strategies has managed to maintain low TTI prevalence in donated blood. There are comparable efforts in blood process, testing and distribution activities. The support services such as haemovigilance, research and development activities are greatly comparable though the outputs magnitude will differ depending of the level of investment.

CONCLUSION

Our findings seems to suggest that despite the differing income status of countries, given the proper strategies blood services in low resources settings can make comparable achievements

INTRODUCTION

World Health Organisation (WHO) regularly provides universal guidelines to member states on the need for blood safety and availability and how this can be achieved nationally.¹ These recommendations are considered and implemented by countries; however, the level of implementation depends not only on commitment but available resources needed to optimise blood safety. There are published blood safety status reports by WHO through Global Database on Blood Safety (GDBS) for categories of low/medium/high (LMH) income status of countries.²

To further comprehend countries blood safety status between LMH income countries a detailed analysis is warranted to enable better appreciation of the underlying contributing factors. In this study the aim was to assess the blood safety strategies of a low human development (LHD) index, Zimbabwe, which is ranked 172 out of 187 and a very high human development (HHD) index, Netherlands, which is ranked 4 in the world.³ The focus is to understand the blood safety strategies and determine the driving forces pushing or threatening sustainability of these Services in their settings. This study recognises that the socio-economical environment of these Services differs substantially and hence restricts the analysis of the strategic options available for optimising blood services, which may be not be applicable to both settings.

METHODS

A study visit was undertaken to Sanquin Blood Supply in The Netherlands in February and March 2014. A transfusion clinical internship was conducted at Martini Ziekenhuis / Hospital, Groningen, Netherlands. The findings from this study visit were compared with equivalent data from National Blood Service Zimbabwe (NBSZ). The data used was obtained through key informant discussions with executives and senior staff at Sanquin and review of the annual performance data as reported in Sanquin annual reports, which are publicly available.⁴ Similarly, data from NBSZ is publicly available from annual reports⁵ and author's experience and knowledge of working and interaction with NBSZ. Data was collected using Excel spread sheet and then analysed. Key thematic points were summarised from the review of the reports as well as the outcomes from key informant discussions. Lessons learnt and recommendations were drawn for each thematic area considered.

KEY FINDINGS

Description of settings

Sanquin Blood Supply Foundation is a not-for-profit organisation responsible for blood supply in The Netherlands, which has an area size of 41,526 km². The same is true for NBSZ, which has a national mandate to provide all blood requirements in Zimbabwe and which area size is 9.4 times more (390,580 km²) than that of The Netherlands. The country size difference, communication and infrastructure present differing challenges for blood donor access to donation sites and hospitals blood accessibility from respective distribution sites. The population of Netherlands is 16.7 million, the majority of who are adults, which is 27% higher than Zimbabwe population at 13.1 million, who are predominately youth. These population structure differences also pose different challenges in blood safety programmes.

Management and Organisation

Both Services are similarly structured with Boards in place (Supervisory Board for Sanquin) and Executive Management Committee (Executive Board for Sanquin). The Boards have the overall responsibility for monitoring the organisation's operations. There are Board sub-committees in both settings. Sanquin has

five divisions; Blood Bank; Plasma Products; Diagnostic Services; Reagents and Research. In comparison to NBSZ, which has departments of Medical Services; Laboratory Services; Finance; Human Resources and Administration; Public Affairs; Quality, Safety, Health and Environment; Planning, Information and Research. It was noted that the functions comprising finance, human resources, administration, planning and Information Technology Communications are placed under corporate staff/services at Sanquin and they provide support to the divisions and advice the Executive Board. With the exception of plasma products and diagnostic services the organisation and management functions are comparable. How these functions are divided is guided by the strategic thrust for the period and the turnover (for Sanquin) hence these fluid structures allow the Services to respond to varying needs and adjust operations accordingly. Currently Sanquin is undergoing centralisation and this may demand further merging/demerge of divisions. NBSZ, on the other hand is seeking possible options for regional Plasma Contract Fractionation of its blood products, which may raise the question of a separate collection facility and donor panel for collection of high quality and adequate plasma volumes suitable to meet international standards required by Regulators for acceptance by an approved fractionation facility. The idea of corporate staff/services for the over-arching staff is one that may be worth considering for NBSZ so that the departments are streamlined into key business units for the main business focuses.

There is a shared need to engage and constantly inform stakeholders, as demonstrated by existence of the informative, interactive and educative websites of both Sanquin and NBSZ. This is a good practice that needs to be maintained. On both websites annual reports^{4,5} of the Services are available, which allows interested stakeholders easy access to relevant donor and blood safety information. The media is strongly engaged in both settings, which helps to promote the Service's brands. This high level of transparency is crucial to the sustainability of these services, which depend on voluntary non-remunerated donors and public perceptions.

The emphasis on blood safety for both the donors and patients is at the heart of the organisations as indicated in their mission statements, vision and core values.^{4,5} There is recognition in both settings that cost-effectiveness should be at the core of operational considerations. Sanquin is aiming to cut cost by 6% by 2015 (11.6 million Euro) through centralisation and operations realignment (staff rationalisation) due to the declining trend in blood usage. NBSZ is pursuing similar cost cutting measures though the performance of the cost containment committee needs to be strengthened as this same trend is taking place in Zimbabwe, where demand is declining. Though the declining trend in the demand and clinical use of blood is similar, the underlying factors may be different. In Zimbabwe it is mainly due to availability and affordability and the financially constrained healthcare system; whereas in The Netherlands, this is attributable to continuing education of clinicians on appropriate clinical use of blood and effective haemovigilance. This area of clinician's education and training is important and NBSZ is in the process of rolling out education and training, within the current financial limitations. It was noted that in The Netherlands, although there is decline in the demand and use of red blood cells, there is an increase in the demand and use of plasma derived medicinal products (PDMPs). This change in patterns of use requires a review of structures and functions in a more cost-effective organisational and management model. One model could be to consider collection of sufficient quality plasma to meet national needs through plasmapheresis of source plasma.

Donor mobilizations and blood collection

NBSZ and Sanquin rely on 100% voluntary non-remunerated blood donation as recommended by WHO¹ to meet National requirements of labile blood products. Meeting the National requirements for PDMP from recovered plasma used for fractionation, that is plasma recovered from whole blood donations and used to produce PDMPs, has reportedly fallen short in nearly every country in the developed world and may presently not be feasible in low income countries. Annually, Sanquin, collects blood from approximately 400 000 donors, compared to approximately 50 000 active blood donors in Zimbabwe, as reflected in the data collected between 2009 and 2012. Over the same period, the annual whole blood (WB) donations in Netherlands averages 540 000 from this donor base, compared to 60 000 units from the donor base in Zimbabwe. This results in 24 donations per 1 000 inhabitants in The Netherlands and 4 donations per 1 000 population in Zimbabwe. WHO's estimate for national blood adequacy is 10 donors per 1 000 inhabitants. If Zimbabwe were to adopt the guideline recommendations set by WHO, this would result in unacceptable expiry of blood and a drain on limited financial resources. NBSZ is currently developing strategies to ensure a sustainable national blood service, which can provide a safe, accessible, adequate and affordable unit of blood and at the same time address the goal of working towards developing a model for sourcing plasma using plasmapheresis in order to meet international standards of safety and sufficient volumes for contract fractionation. A blood donor in Netherlands donates at least 1.6 units of WB annually versus 1.8 units in Zimbabwe. This frequency is interesting, as it provides an impression that donor retention in Zimbabwe is higher than (or at least comparable) to Netherlands. However when one looks at other retention measures then the apparent differences become clearer. If the percentage of repeat donors per year is examined more closely, it becomes apparent that in the Netherlands this is approximately 90% versus 56% in Zimbabwe. On average, 53% of donors in Zimbabwe provide at least two usable units and the corresponding figure from Netherlands was not readily available from the Annual Reports (but presumed to be greater than 80%). Further, in Zimbabwe the year-to-year donor retention is on average 34% and the corresponding data is not readily available for Netherlands (but presumed to be greater than 80%)

Donor retention is a critical indicator of donor management and each Blood Service should attempt to use a standard definition. This assessment indicates that to use only average donations as an indicator of donor retention may be inappropriate especially when there is need to compare different settings. It may be worthwhile for Sanquin to consider to expand their donor retention measures and report on these as explained above.

In Zimbabwe donations are either WB or apheresis for platelets (about 150 annually). In Netherlands there are WB, apheresis (plasma and platelets) donations (about 325 000 annually). Due to lack of plasma market in Zimbabwe the majority (75%) of this is discarded and this is despite the fact that there is severe shortage of plasma derivative products in Zimbabwe. Concerted efforts are needed in Zimbabwe to ensure that plasma is used for plasma derivative production to help the need patients in Zimbabwe and we note that NBSZ alone has no capacity to address this problem as it needs to meet the good manufacturing practice (GMP) requirements for the plasma supply. This would require the involvement of Government of Zimbabwe and all international partners. There is an opportunity for NBSZ to expand apheresis services further for patient management as observed at Sanquin. This will be additional possible source of revenue and also helps to maintain the staff skills.

On average 10% of donors are new donors in Netherlands compared to 44% in Zimbabwe. This large disparity is due to the fact that in Zimbabwe, about 70% of collections come from donors aged 16-20 years old. These are highly mobile donors hence the loss rate is high. This also affects donor retention as discussed earlier. The donors in Netherlands starts donating at 18 years and are mainly composed of adult donors who are stable hence easier to retain. NBSZ need to pursue its strategy to re-align the donor base to a more sustainable structure balanced on youth and adult base. In both settings there are incentive schemes that assist in the retention of donors and these need to be maintained. The desire for Netherlands to increase youth donors may benefit from the NBSZ pioneered successful youth projects that consist of the peer promoters and the Pledge 25 Club that has since been copied all over the world.^{6,7}

The blood safety measures for the new donors are comparable. In Netherlands all new donors undergo medical examination first and a sample is provided for transfusion transmissible infections (TTI) testing and blood typing. If a donor is cleared from this initial assessment, then they are called within two weeks to provide their first-time donation. In Zimbabwe, new donors are risk profiled historically based mainly on age at donation. New donors aged 16-20 and those above 45 years provide usable blood. For those donors aged 21-44 years old, an unusable blood is collected (a blood pack without anti-coagulant).⁸ In both settings these are all measures to safeguard blood supplies and informed by risk considerations and settings practicalities. In Zimbabwe where 80% of donors are at mobile clinics and the mobile drives might be about 300km, the Netherlands blood safety management model may be difficult to implement. These variations based on the need to optimise blood safety have the inevitability of resulting in different definitions of new donor or first-time donor. One may argue that the first-time donation in Netherlands is not really 'first' as logically this is a 'second' interaction with the donor. The statistical challenges that arose from this scenario are obvious. It will become critical then that further definitions to capture these variations are developed and reported on so that there will be consistency and comparability of data definitions in different settings.

Blood processing and testing

In both settings there is production of components that includes at minimum RBC, FFP, Cryoprecipitate and platelets. The production systems are comparable, but in Netherlands the product lines are quite varied compared to Zimbabwe. This gives patients more choice of available products.

There is testing of the four TTI markers (HIV, HBV, HCV and Syphilis) universally recommended by WHO.^{9,10} NAT is used in Netherlands and in Zimbabwe 4th generation serological testing technology is in use. Additional test are done in Netherlands including HTLV, which since 2013 is only being tested in new donors as a cost-containment measures which is also informed by the fact that the production process reduces the infection level substantially. This is important as the available best evidence guides operations. ABO and Rhesus typing are done but there is more extensive typing in Netherlands. The donor blood group distributions are comparable with Sanquin having 48%, 39%, 9% and 3% (NBSZ, 52%, 25%, 20%, 5%) for O, A, B and AB blood groups respectively. There is more typing (forward and back typing) of new donors (sample have different cap colour, also multiple sample sources are used) in Netherlands and this substantially reduces blood group discrepancies for the donor current and future donations.

Zimbabwe may need to consider this Netherlands approach to reduce the current high number of blood group discrepancies that has been observed. In both settings, testing is centralised at one facility and this ensures similar testing quality standards nationally. The prevalence of four universal TTI markers in donated blood averages (2005-2012) per 100 000 for new (n) and repeat (r) donors as follows in Netherlands for Syphilis (n=31.9, r=2.8; Zimbabwe, n=411.1, r=194.4); HCV (n=17.1, r=0.2; Zimbabwe, n=190.1, r=84); HBV (n=52.1, r=1.6; Zimbabwe, n=1645.4, r=366.7); HIV (n=3.8, r=0.5; Zimbabwe, n=681.2, r=229). It is important to note the serological testing algorithms are similar, however in Netherlands there is use of NAT and there is confirmatory testing using western blotting and PCR. In Zimbabwe, the confirmation is done using an alternative but comparable (sensitivity) testing assay. Despite the general population epidemiological differences of these TTIs in both settings, the donations testing results may also need to be cautiously interpreted taking these testing variations into considerations. It was noted that the issue of indeterminant results is prevalent in both settings. Consecutively (three times) indeterminant donations from the donor would result in permanent donor deferral in Zimbabwe and in Netherlands an indeterminant results from a new sample collection would lead to the permanent donor deferral. The challenges of communicating the indeterminant results and deferral decision to donors are similar but keeping them on donor list would waste resources as indeterminants will still 'pop-up' and products are unusable. NBSZ current efforts to do further research on indeterminants may draw lessons from Sanquin experience which do the confirmation and still the donor results remains indeterminant. Under those circumstances, the logical decision for NBSZ is pursue and maintain its permanent deferral policy. In both setting, post-donation counselling services are provided. In Sanquin, medical doctors and state registered nurses do this and counselling partners are used in Zimbabwe.

In the Netherlands, the non-serological discard rate is 0.2% and 0.4% (2012) for the serological waste. This is in contrast to Zimbabwe where the non-serological discard can be as high as 8% and serological wastage is around 1.7% (2012). There are opportunities to further reduce the discards in Zimbabwe especially on the non-serological discards to the below 2% threshold recommended by WHO as blood expiries constitute the bulk of the non-serological discards. The high serological discards in Zimbabwe might be a reflection of equally high TTI prevalence in the general population especially for HIV and HBV despite all the stringent pre-donation selection interviews. It is important to note that in Zimbabwe the discard rate for HBV is twice that of HIV, which may be a reflection of either a high general population HBV prevalence (not well studied) or that the current risk factor exclusion is not very effective for HBV or perhaps its the testing HBV dynamics. This demands further understanding of whether this can be reduced further.

Distribution of blood and blood products

In both settings there is inventory management system in place. There is opportunity to use distribution data to inform blood collections on shorter periods in Zimbabwe and this will help to moderate supplies to avert wastages and intermittent shortages. Having a dedicated logistics inventory management appointment might be useful in Zimbabwe to strengthen this area as observed in Netherlands. The Sanquin Blood Supply cold chain consists of simple to use but effective cold chain equipment consisting of cooler boxes, cooling trays and packs. Such simple low-cost may be considered in Zimbabwe settings.

Sanquin delivers blood to hospitals in contrast to Zimbabwe where hospitals are responsible for their own blood collections. It has been argued that the Netherlands supply system may not be cost effective as indications are that hospitals may not be strategically ordering blood to minimise delivery trips as Sanquin bears this once off cost. Mechanism to enforce hospital to make structured cost-effective ordering schedules may be required in the Netherlands. In both setting the cost of blood and blood products is an issue that attracts political, media and public scrutiny. The principled position that has been taken by the Services, which are commensurate with the expected level of blood safety, needs to be maintained. Blood safety should be the main considerations first and how this can be financed will be a matter of all partners' engagements.

Quality Assurance

In both settings quality assurance is at the forefront of operations. Formal quality recognition is being pursued or maintained at these Services. It was noted that Sanquin ceased its formal recognition of ISO 9001 on quality management systems partly because of cost considerations and the need to be guided by EU directives, which are continuously monitored by government. It remains a point of discussion on whether formal quality management systems being pursued in Zimbabwe need to be maintained or focus should be directed to meet applicable GMP requirements for blood establishments that has the potential of opening plasma market opportunities in Zimbabwe.

There is strong emphasis in both settings that quality management system should be embraced and owned by all staff. We noted the organisational management differences with respect to quality management systems that might need to be considered further.

Research, Education and Training

The quest for evidence based decision-making process in both settings is noted through their vibrant research programmes. Sanquin research program is more mature and has outputs at high levels with 12 PhD theses and 175 peer-reviewed publications just in 2012. The current transfusion research capacity (T-REC) building project in which NBSZ is a partner is increasingly building a strong base for scientific research and these needs to be maintained. It was noted that NBSZ need to promote its research outputs more through say highlighting these on its website and systematically evaluate how past research efforts have been used to strengthen blood safety policies in Zimbabwe.

Sanquin has various training programmes in place both internally and collaboratively. There is need to maintain contact on training opportunities in both settings especially on the masters programme that is being developed for donor health management. Continual sharing of resources and experience will also assist both Services to appreciate the emerging trends in blood safety.

Information/Data Management Systems

Both settings use commercial information management systems to manage blood banking data (eProgressa in Netherlands and eDelphyn in Zimbabwe), which is available on wide area network. There are other complementary databases in use in Netherlands for Hemovigilance, laboratory testing and quality management systems that are linked through servers for data sharing and repositories. There is opportunity for NBSZ to consider such other complementary databases, which may assist mainly in hemovigilance and quality management systems (strive towards paperless).

Given the huge amount of data the Services generate, it was a discussion point on whether the data management/use can also be enhance through a data management function that would assist all departments in Sanquin as is the current position in Zimbabwe.

Clinical transfusion medicine

In both settings clinical blood transfusion is guided by the blood transfusion guidelines. It was noted that in Netherlands all key stakeholders jointly author and publish these guidelines and this enhances ownership and compliance to the standards. The Martini hospitals have its own transfusion management system that handles internal blood orders and for blood stock management. This hospital system is not yet linked with Sanquin blood information management system and orders are made through fax and phone as necessary. For this hospital, it manages its own blood deliveries from Sanquin and there was evidence of continual engagement of the hospital and Sanquin. NBSZ is pursuing options of linking hospitals to its e-Delphyn blood bank management system and engagement with hospitals are continually being strengthened.

Martin hospital for 2013 had 5 189 red blood cells transfusion, 276 platelets and 395 fresh frozen plasma almost equivalent to the capacity of referral hospitals like Parirenyatwa Hospital in Zimbabwe. The hospital information management system allows analysis of blood usage data as needed and this is currently a challenge in Zimbabwe as most hospitals do not have such shared systems in place. The introduction of electronic temperature management tags allowed about 29 red blood cells to be saved in 2013 after non-usage from the ward based on 30-minute rule. The existing surgery list that suggests how many blood units are to be reserved for each planned operation. This greatly helps in stock management.

The hospital has a hospital transfusion committee in place with participation of Sanquin blood supply staff. All transfusion reactions are reported to TRIP through the established forms. The mature HTCs programme in Netherlands can be useful as a learning point for Zimbabwe to strengthen blood bank and clinical transfusion interface. It was noted that blood service having service level agreement with hospital is critical to ensure interaction and cooperation of the parties.

CONCLUSION AND RECOMMENDATIONS

Despite the differences in income status between Zimbabwe and Netherlands there are several common areas of operations. There exists also further opportunities to share the experiences of two settings as a means of continual blood safety strengthening. It is not the intention to replicate any one Service with another but all decision should be evaluated based on the applicable contextual environment of operations.

It can be concluded that the two Blood Services are doing all in their capacity to improve blood safety. In Europe, Sanquin Blood Supply is at the forefront of blood safety programmes and in sub-Saharan Africa, the blood safety record of National Blood Service Zimbabwe is well positioned. These blood safety leadership roles need to be maintained and complemented with Governments and partner's support. Both Services may benefit from maintaining corporate engagements processes in areas of mutual interest.

Based on the findings the key recommendations for each setting are provided:

Key areas for NBSZ to consider consolidating:

- Diversity revenue stream, the private business entity needs strengthen. The budget of blood banking and the private sustainability initiatives may need to be separated.
- Expand apheresis services for clinical management.
- Establish research laboratory, with equipment to support research and allow resource sharing with partners.
- Strengthen NBSZ consultancy services especially in sub-Saharan Africa. These services will also need to be marketed.

- Enhance education and training and follow-up on the outputs from these initiatives.
- Intensify cost-recovery measures for the blood banking operations. Initiatives like the EU / UNICEF coupon systems that adds directly to the procurement of the blood products is further recommended to be vigorously pursued. This is important in view of the cash-constrained public sector.
- In line with its innovation aspirations, this needs to be strengthened further so that there is documented evidence of innovation products.
- NBSZ to pursue avenues for Plasma Fractionation at various levels (region & WHO).
- NBSZ to intensify its support engagement and place strongly the patient at the forefront in order to strengthen its GMP call for support. As NBSZ it is primarily there for the need patients hence this should form the basis of all strategic engagements.
- Strengthen Hemovigilance system with hospitals and ensure that that there are service level contracts.

Key areas for Sanquin to consider consolidating:

- Broaden the definitions of donor retention calculation and report these.
- Maintain a strong collaborative focus with other blood services and organisations internationally. This will allow further developments in blood safety programmes.
- Pursue and provide strategic leadership internationally on how plasma derivatives may be made available affordably to resource-constrained settings.
- Introduce a data management function at corporate level to coordinate all data repositories and ensure this feeds into the monitoring and evaluation systems of Sanquin.
- Review cost-effectiveness of blood delivery system to hospitals

REFERENCES

1. WHO | World Health Assembly and Executive Board resolutions on blood safety and availability. at <<http://www.who.int/bloodsafety/resolutions/en/>>
2. WHO. WHO | Global database on blood safety at <http://www.who.int/bloodsafety/global_database/en/>
3. UNDP. | Human Development Reports. at <<http://hdr.undp.org/en/countries>>
4. Sanquin Blood Supply. Annual reports, scientific reports and financial statements | Sanquin Blood Supply. at <<http://www.sanquin.nl/en/about/about-sanquin/annual-reports/>>
5. National Blood Service Zimbabwe. Annual Reports and Publications. at <<http://www.nbsz.co.zw/index.php/media-centre/annual-reports-and-publications>>
6. WHO. WHO | Voluntary non-remunerated blood donation. WHO at <http://www.who.int/bloodsafety/voluntary_donation/en/>
7. WHO | 14 June: World Blood Donor Day to honour voluntary, unpaid blood donors all over the globe. WHO at <<http://www.who.int/mediacentre/news/releases/2004/pr39/en/>>
8. Mapako, T. et al. Human immunodeficiency virus prevalence, incidence, and residual transmission risk in first-time and repeat blood donations in Zimbabwe: implications on blood safety. *Transfusion (Paris)* 53, 2413–2421 (2013).
9. Information, N. C. for B., Pike, U. S. N. L. of M. 8600 R., MD, B. & Usa, 20894. Screening for transfusion-transmissible infections. (2009). at <<http://www.ncbi.nlm.nih.gov/books/NBK142989/>>
10. TOC.pdf. at <<http://www.ncbi.nlm.nih.gov/books/NBK142990/pdf/TOC.pdf>>